NEURAL PLASTICITY AND ON, OFF AND STEADY-STATE RESPONSES

THE POSSIBLE CONTRIBUTION OF NEURAL PLASTICITY

TO

ON, OFF AND STEADY-STATE RESPONSES

ELICITED BY BRIEF TRAINS OF REPETITIVE STIMULATION

By

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ABSTRACT

The possible contribution of neural plasticity to ON, OFF and steady state responses elicited by brief, repetitive trains of stimulation was investigated in the intact human subject with the use of the electroencephalogram (EEG). Experiment One implemented trains of stimulation at three different repetition rates, 1.5Hz, 4Hz and 13Hz. The goal was to investigate the nature of the ON, OFF and steady state responses evoked at these repetition rates. The experiment was carried out in three modalities: visual (n=13), auditory (n=10) and somatosensory (n=12). The main result was that the ON and OFF responses were enhanced at 13Hz compared to the lower repetition rates. Experiment Two sought to answer the question of whether enhancement depended on the repetition rate or the increased experience provided by the higher frequencies. The number of stimuli in the 13Hz trains was reduced to equal the 1.5Hz condition from Experiment One. Graded exposure was then provided to the 13Hz stimulation. This procedure was implemented in two groups of subjects: Replication One (n=12) used 13Hz stimulation and Replication Two (n=24) used 14Hz stimulation. A subset (n=10) of the Replication Two subjects returned for a second session (Day 2) 24 hours after the first. An assessment of effects was made after minutes and hours. There were four main results. The OFF response was observed after nine 13Hz pulses and did not change over the course of the experiment. The ON response increased with exposure to the 13Hz trains. Steady state responses diminished and showed a phase shift over the experimental session. Results for Day 1 and Day 2 were not different. Within session changes, as a result of exposure to the stimulus, were seen. These effects were not long lasting.

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TABLE OF CONTENTS

LIST OF FIGURES

CHAPTER ONE

INTRODUCTION

Neuroscience is faced with the challenge of understanding the neural mechanisms that are responsible for cortical plasticity and reorganization (Buonomano & Merzenich, 1998). The goal is to discern how behavioural experience alters the functional circuitry of the cortex and hence, changes the way the cortex processes information (Cruikshank & Weinberger, 1996). It has long been accepted that many changes take place in the cortex during development; the brain is mutable and affected strongly by the environment during critical periods early in life. It was thought that after this time, sensory systems were stable and processing was fixed. However, it has now been shown that adult cortical representations are not fixed. Primary sensory cortices have the constant ability to change with experience. Understanding how the circuitry of the cortex is altered with experience will help understand the more adaptive processes that the cortex achieves such as learning and memory (Cruikshank & Weinberger, 1996).

Plasticity in Adult Sensory Cortices

Early findings of plasticity stemmed from work done on amputation (Calford & Tweedale, 198l; Ramachandran et al., 1992), nerve transection (Kalaska et al., 1979; Merzenich et al., 1984) and lesions of the sensory epithelium (Kaas et al., 1990, Gilbert & Weisel, 1992). Sensory deafferentation, by any of these means, usually resulted in the

area of cortex that was deprived of its normal input changing its responsivity to areas of cortex adjacent to the site of deafferentation. For example, Robertson & Irvine (1989) lesioned the cochlea of adult guinea pigs and, 35 to 81 days later, examined the cortex that represented the lesioned frequency. The cortex was not inactive but rather, was occupied by an augmented representation of the frequencies that were bordering the frequency range that was lost due to the lesion.

More recently, plasticity research has focussed on behavioural experiences, training subjects on behavioural tasks or changing the subjects' experience with the environment, that lead to plasticity. Experience dependent plasticity has been seen in the visual (Karni & Sagi, 1991), somatosensory (Allard et al., 1991; Diamond et al., 1994; Wang et al., 1995) and auditory cortex (Edeline et al., 1993; Pantev et al., 1998) of mature and intact adult subjects. Recanzone et al. (1993) trained owl monkeys in an auditory frequency discrimination task for several weeks. Monkeys learned to differentiate small differences in tones presented in succession. In addition to improvements in discrimination performance, the monkeys showed a greater cortical representation of the trained frequencies than was seen at the same frequencies in passively stimulated control monkeys. Most experience dependent plasticity has been documented after weeks (Wang et al., 1995), months (Recanzone et al., 1992) or years (Elbert et al., 1995).

However, recent evidence indicates that cortical networks can be altered on a much shorter time scale. Diamond et al. (1994) studied the effects of correlated input from a rat's whiskers. All whiskers were shaved with the exception of two and the rat

was left in its home cage for 24hours. A measurement at this time showed that the neurons tuned to one of the whiskers now had an increased firing rate to the neuron with which it was paired. The increase in response was not seen to other unpaired whiskers or in control animals. Changes in the response of neurons were seen after hours rather than weeks, months or years.

Bakin & Weinberger (1990) used frequency-tuning curves to study learning and memory after brief exposure to a classical conditioning paradigm. Adult male guinea pigs were used to study the frequency tuning properties of neurons in primary auditory cortex. The pre-training receptive field was measured, using 11 spectral frequencies that were different for each animal but remained constant within animal, to determine the response activity to different tones. A tone was chosen as the conditioned stimulus (CS) that had elicited an identifiable response at some intensities, but did not elicit a maximal response at most intensities. Conditioning trials involved a 10s 80dB tone (CS), followed at tone offset by a 2s shock (US). Animals received 10-30 trials of paired stimulation. The conditioning trials quickly resulted in a very specific change in the tuning preference of the neurons. For one animal, the pre-training best frequency (BF) was 9.5kHz and the CS was chosen to be 9.0kHz, approximately 1/10 of an octave away. Conditioning led to a maximal increase at the CS frequency and a maximal decrease at the original BF. This was true of all animals that exhibited change. Overall, conditioning resulted in CS frequency-specific increases in the tuning of auditory neurons in 70% of the cases. The receptive field plasticity was present at retention intervals of 1hr and 24hrs. The tuning was very selective, as was the case in the auditory frequency discrimination by

Rencanzone et al (1993), yet the animals did not have to make any discriminative judgements. The change in tuning was seen after 10-30 conditioning trials, which equates to only minutes of experience with the stimuli. The authors note that this is a rapid form of plasticity but it still "may be a substantial underestimate of how quickly RF (receptive field) are modified during learning" (p.283).

Experience dependent plasticity, regardless of the time scale, has usually been induced by "associative" procedures. Examples of such procedures are skill training, sensory discrimination and classical conditioning. All of these procedures involve an explicit correlation between sensory input and behaviourally relevant task events. However, "non-associative" procedures, which expose subjects to repetitive sensory stimulation under conditions of attention, can also lead to changes in neuronal response (Marlin et al., 1991; Condon & Weinberger, 1991; Tovee et al., 1996).

Tovee et al. (1996) examined the firing rate of single visual neurons to ambiguous and unambiguous images. There were three blocks of stimulation: 1) ten 0.5 second presentations of the ambiguous image; 2) ten 0.5 second presentations of the unambiguous image; and 3) ten 0.5 second presentations of the ambiguous image. Each of the ten presentations was interleaved with control images. The result was that the response of the neurons to the ambiguous image in block 3 was increased by exposure to the unambiguous form in block 2, with no change in response to the control images. Visual cortical areas were rapidly modified by experience in the range of 5-10seconds. The changes resulted not from a pairing of a CS and US or discriminative judgements, but solely from increased experience with the stimuli.

Condon & Weinberger (1991) studied habituation of neuronal response in the auditory cortex. Habituation is a decrease in response to a repeated stimulus. Condon & Weinberger posed the question of whether this decrease was due to a general reduction in neuronal excitability or to a change in the way the stimulus was processed. A sequence of 24 tones was presented 10 times to adult guinea pigs while neuronal discharge was recorded. An initial frequency receptive field (RF) was measured and the RF was determined to be stable before the procedure began. A frequency that elicited a response, but did not have to be the best frequency in the sequence was chosen for use as the repeated stimulus. Subjects were then exposed to the single chosen tone 390-540 times. The RF was determined following this exposure. The overall result of the repetitive stimulation with one tone was that the RF showed a decrease (72% of the time) in neuronal firing to the frequency of the repeated stimulus. Increases to the tone were seen 8% of the time and 19% of the subjects showed no change. The change was very specific with little or no change occurring to the other frequencies in the sequence. As well, the authors report an effect of incubation; the frequency-specific decrements continued to develop (they were not at a maximum when RF was measured immediately after repeated tone exposure). Therefore, changes could not be due to adaptation or fatigue, otherwise the maximum decrease would be seen immediately after exposure. The authors conclude that stimulus repetition produces frequency-specific plasticity in the RFs of neurons in the auditory cortex. Habituation, a non-associative form of learning, "shares with classical conditioning the property of altering the processing of information in the representation of frequency at the level of auditory cortex" (p.429).

Plasticity has, therefore, been demonstrated on a rapid time scale and as a result of simple stimulus repetition. The experiments reported in this thesis investigated whether highly plastic phenomena contribute to the development of simple sensory representations reflected in the human electroencephalogram (EEG).

Sensory Representations and EEG

The generalized activity of the cerebral cortex can be measured in the intact human subject with the use of EEG. Network dynamics, on a very large scale, are reflected in scalp-recorded fields. Sensory stimulation evokes various potentials in the visual, auditory and somatosensory modalities. Transient responses occur when the brain has had time to recover between stimulus presentation, whereas if the brain response to successive stimuli overlap, the response is considered a steady state response (Regan, 1989)

Transient vertex responses in various modalities, though not identical, are similar in waveform, amplitude, latency and recovery period (Davis et al., 1972). Transient responses to stimulus onset typically involve a waveform with a vertex-negative (N1) response between 50 and 150ms, and a vertex-positive (P2) response between 150 and 250ms. The OFF response is similar in waveform, at least in the auditory case, to the ON response (Schweitzer & Tepas, 1974), but is found to be about one-third of the amplitude of the ON response (Cody & Townsend, 1973). A figure depicting the N1-P2 complex of the ON and OFF response and the difference in amplitude between the two responses can be found in Appendix I. Pantev et al. (1996) localized the N1 and P2 components of the auditory ON and OFF responses. Though the N1 and P2 components came from

different cortical areas, the N1-ON and N1-OFF were generated by the same source, as were the P2-ON and P2-OFF. Therefore, the ON and OFF responses originate from overlapping cortical sources. These sources have been localized to sensory cortices (Hari et al., 1987).

Other studies in the auditory domain showed that longer tone duration resulted in a larger OFF response and that the amplitude of the ON response decreased when followed more closely by an OFF response (Pfefferbaum et al., 1971). Because ON and OFF responses appeared to require a stable sensory foreperiod on the order of 500 msec for their occurrence (Hillyard & Picton, 1978), it has been suggested that ON and OFF responses are indicative of an underlying system that represents and detects changes in the sensory environment (Hillyard & Picton, 1978).

Some time on the order of 200-500ms is required to capture the stimulus. That is, transient ON and OFF responses can be separately observed if there is 500ms between stimulus onset and cessation (Pfefferbaum et al., 1971). These effects have been reported after averaging of several hundred epochs. Is plasticity involved in developing a representation of the stimulus? To address this question, the experiments in this thesis investigated whether transient and steady state responses changed with sensory experience, and if so, whether the changes persisted over time, suggesting that a memory of the stimulus had been formed.

CHAPTER TWO

EXPERIMENT ONE

A wide range of flash frequencies (0.3 to 40Hz) was used by Bullock et al. (1994) to study the visual OFF response. There was a difference in morphology of the response seen below 2Hz compared to that seen above 5Hz, with no reported OFF response between these two frequencies. Hence, the OFF response was dependent on repetition rate. Experiment One, inspired by Bullock's study, posed the question: what is the nature of the ON, OFF and steady state responses elicited by trains of stimulation presented at different repetition rates? The experiment used 6second trains of stimulation at three different repetition rates separated by 2second gaps. The visual, auditory and somatosensory domains were studied.

If, as suggested above, ON and OFF responses are detecting changes in the sensory environment, perhaps these responses can be used to examine how the cortex goes from representing novel stimuli to stimuli with which it has gained experience. Following from Experiment One where novel trains of stimuli are presented, Experiment Two measures the effect of experience on the ON, OFF and steady-state responses in the visual domain. More specifically, it seeks to answer how these responses change with graded exposure to the stimulus. The effects were examined after minutes and hours. This is an attempt to track rapid plastic changes in adult humans in a non-invasive way.

METHODS

Subjects

The subjects were 35 student volunteers, 21 females and 14 males, from McMaster University. All volunteers were unpaid and most participated for course credit in Psychology 1A3 or 1AA3. The age of the subjects ranged from 18 to 35 years of age.

Materials

Electrode caps were used that had an array of Sn electrodes. The array covered frontal (Fp1, Fp2, F7, F3, Fz, F4, F8), central (T3, C3, Cz, C4, T4), parietal (T5, P3, Pz, P4, T6) and occipital (O1, O2) sites and was in agreement with the international 10-20 system. As well, ear electrodes were used for recording. The reference electrode was Cz and the ground was at a site between Cz and Fz. The skin below each electrode site was abraded and the electrode cavity was filled with Electro-Gel to lower the impedances below 5 ohms. The data were collected with a 32 channel Synamps EEG (NeuroScan Inc.). The recording was continuous with a sampling rate of 1000Hz. The filter for data acquisition was set at DC to 200Hz.

Three groups of subjects were used in Experiment One. The groups were presented with either visual (n=13), auditory (n=10) or somatosensory (n=12) stimulation. The stimulation for the visual condition was a light emitting diode (LED). LEDs have been proven to be simple, low cost and effective visual stimulators (Mushin et al. 1984). The LED used in this experiment had a diameter of 14mm and produced 10ms bright red flashes. The auditory stimulation was a 1kHz tone presented in 10ms

tone pips with a rise and fall time of 2ms. The tones were given binaurally to the subject from a speaker placed on a table in front of the subject in the experimental room. The stimulation for the somatosensory condition involved a 2mm non-ferrous tactile probe, which delivered tactile pulses in 10ms bursts to the index finger on the right hand. The probe was driven be a solenoid housed in a mechanically and electrically shielded covering.

Procedure

Subjects were seated in a dimly lit room in a high back chair. They were instructed to remain still and to blink as infrequently as possible. In the visual condition, the subject was seated approximately one meter from the LED. The LED was positioned so that the flash was landing directly between the subject's eyes. Subjects were positioned one meter from the speaker in the auditory condition. In the somatosensory condition, the subject's arm rested on a foam piece while their index finger rested on the stimulator.

Subjects were asked to keep their eyes open throughout the experiment. Somatosensory subjects wore headphones delivering white noise to mask any artifact arising from the mechanical stimulator. Use of the white noise in the visual condition was for the purpose of consistency only. Obviously, auditory subjects did not receive white noise in order that the tone pips could be properly heard. Once the recording began, the session lasted approximately 55 minutes.

The within-subject variable under study was frequency of stimulation. There were 3 different stimulus conditions presented to each subject: 1.5Hz, 4Hz and 13Hz.

Each frequency was presented in trains of 6 seconds ON and 2 seconds OFF. The OFF was timed from the first omitted stimulus. Each train resulted in a different number of stimulus presentations for the three different frequencies. The subject experienced 9 pulses per train at 1.5Hz; 24 pulses at 4Hz; and 78 pulses at 13Hz. The order of presentation was as follows: 40 trains at 1.5Hz; pause; 40 trains at 4Hz; pause; 40 trains at 13Hz; and pause. This was repeated for a total of three times, resulting in 120 trains of stimulation per frequency per subject. Subjects were instructed to count the number of pauses, or OFF times (the 2 second gap, timed from the first omitted stimulus, at the end of each train), and this number was reported to the experimenter at the pause before the next rate. The purpose of this instruction was to ensure that the subjects maintained attention to the stimuli. The subject's ability to correctly count the number of pauses was quite good and the report of the counts given by the subjects for each block can be found in Appendix II. The stimulation period, off period, blocking order and instructions all remained constant. Each subject experienced the above procedure in one of the three modalities while their EEG was recorded.

Signal Analysis

A 4300ms epoch was created from each subject's data. The epoch captured the following areas: the last 1500ms of stimulation, the 2 seconds of "off" time and the first 800ms of the next stimulus train. Artifact rejection, set at -100uV to +100Uv, was based on the Fp1 and Fp2 electrodes. An average of the accepted trains, out of a possible 120, was determined at each frequency for each subject and given a common reference. The re-baselining and filtering were determined by the type of response being investigated

(ON versus OFF response; transient versus steady state response) and will be reported where necessary.

It should be noted that for the somatosensory stimulation, there was a delay between the trigger and the tactile pulse. The subject received the tactile pulse 12ms after the trigger was sent to mark stimulus onset. This is not corrected for in the somatosensory figures.

RESULTS

A) OVERALL PICTURE

The grand averages for each modality are presented below in Figures 1, 2 and 3. Each subplot represents a frequency. The two vertical lines denote the time of the first omitted stimulus (-2000ms in the figure) and the onset of the next train of stimuli (0ms). An array of electrodes (FZ,C3,CZ,C4,PZ,O1,O2) was chosen for presentation that captured the largest response at each modality, as well as represented the whole head sufficiently. The data were re-baselined to the last 100ms before stimulus onset (-100ms to 0ms) and were filtered with a finite impulse response (FIR1), zero-phase shift, low-pass digital filter set at 50Hz. All data were given a common average reference.

Figure 1 - Visual Grand Average (n=13)

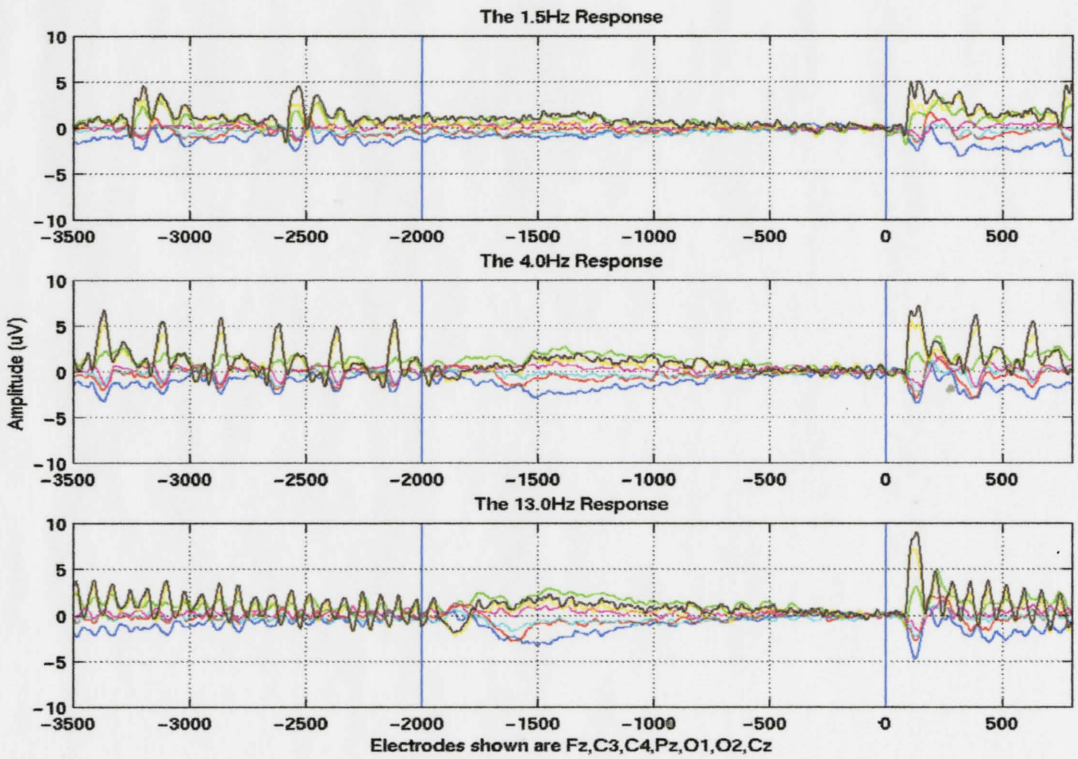


Figure 2 – Auditory Grand Average (n=10)

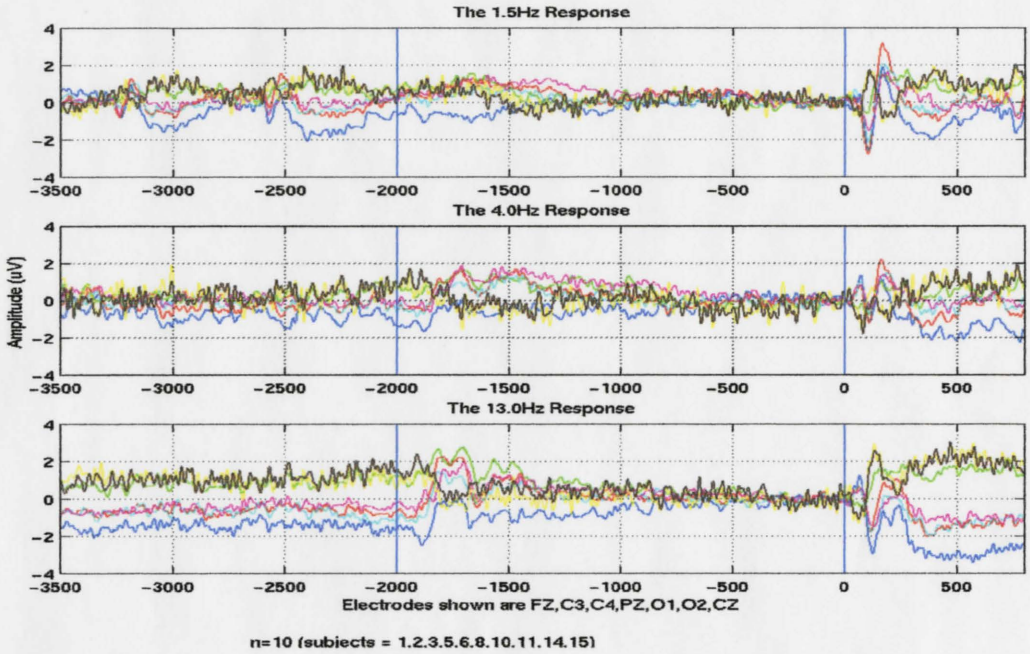
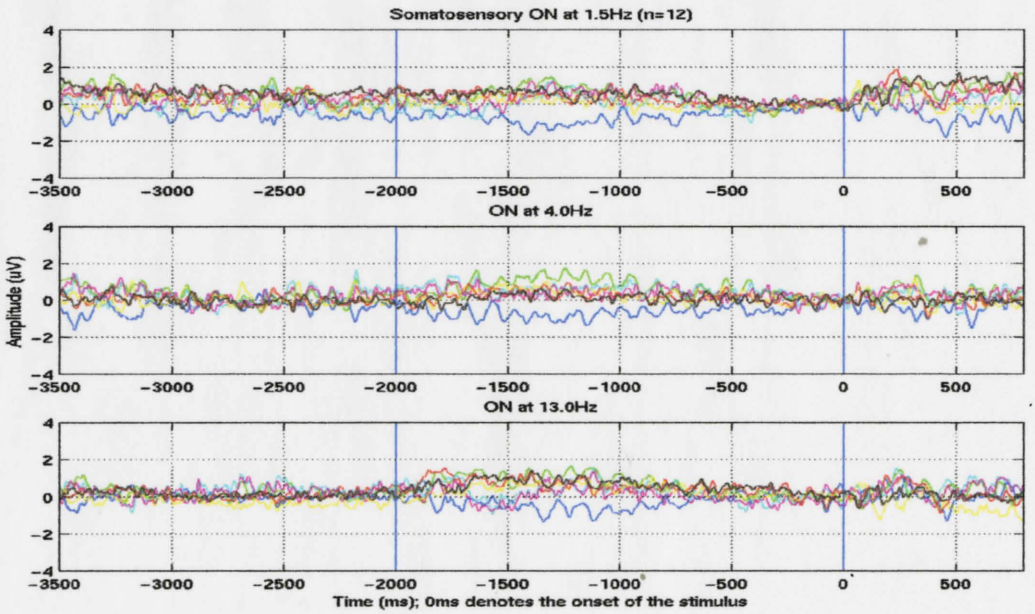


Figure 3 – Somatosensory Grand Average (n=12)



ON and OFF responses were seen in each modality. The figures show that ON responses were seen at all frequencies for all modalities though the ON response was less pronounced in the somatosensory case. A complex OFF response was apparent at 13Hz in all modalities and appeared to develop across frequencies. At 1.5Hz, it was hard to argue that an OFF response occurred at the end of the train but this argument became more convincing as the frequency was increased.

The visual data (Figure 1) had the best signal to noise ratio and as a result provided the most precise picture. In addition to the ON and OFF trends described above, the area depicting the end of the train (-3500ms to –2000ms) showed transient events at 1.5Hz and steady state pulses at and above 4Hz. The auditory data (Figure 2), though not as clear as the visual data, showed definite ON responses and the development of the OFF. These effects were less obvious in the somatosensory data (Figure 3).

B) VISUAL DATA

Analyses were concentrated in the visual domain and most of the discussion will be drawn from there. There were several reasons to focus primarily on the visual data. As mentioned previously, the best signal to noise ratio was acquired in the visual domain. The work by Bullock et al. (1994) describing dynamic properties of evoked and omitted stimulus potentials was conducted solely in the visual domain. As well, Experiment Two, which sought to investigate whether rapid forms of plasticity were contributing to the development of the responses to be described here, implemented visual stimulation only.

i) ON and OFF Responses

Figure 4 – Visual ON and OFF Responses Across Frequency

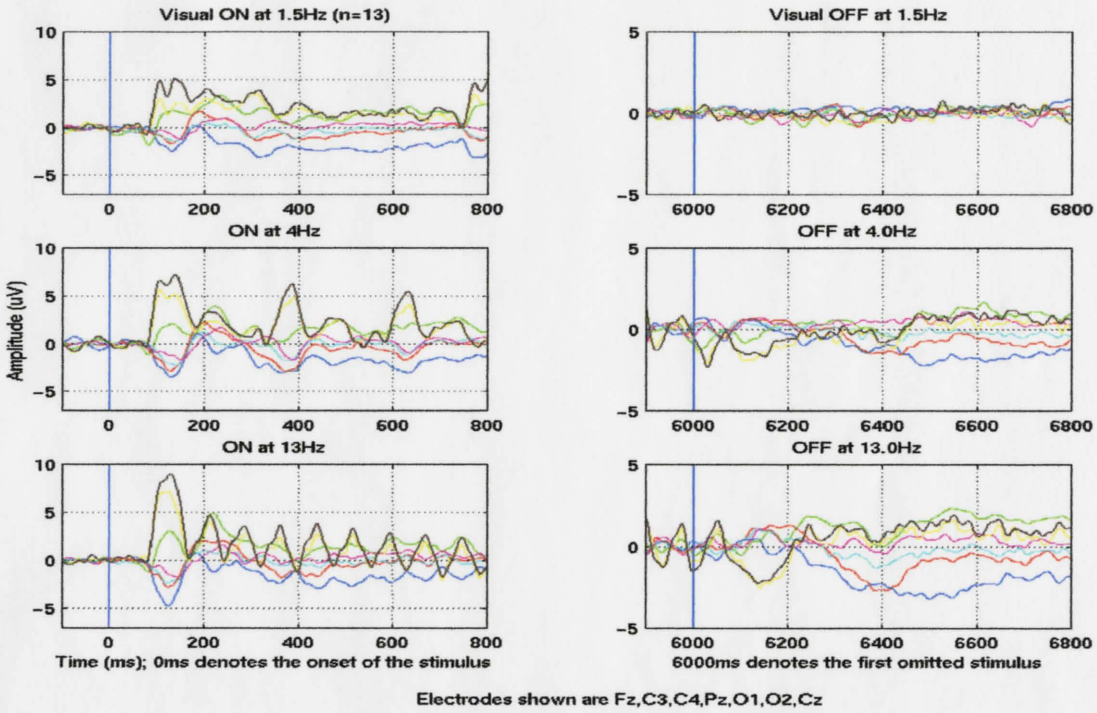


Figure 4 focuses more closely on the ON and OFF responses seen in the visual grand averages for each frequency. It is intended to highlight two main points. First, the main positive component of the ON response appeared to become larger as frequency was increased, with the ON becoming more dipolar overall. Second, the OFF response developed as frequency was increased. The ON data were re-baselined to the last 100ms before the onset of the stimulus, while the OFF data were re-baselined to the last 100ms before the first omitted stimulus. Other processing was as described above.

T-tests

It must be noted that the approach taken here was descriptive and the following t-tests were done to look for consistency in the results. A conservative level of significance was adopted ($p<0.01$,two-tailed) but no correction was made for multiple comparisons. The occipital leads were averaged together for each subject and examined at 1.5Hz, 4Hz and 13Hz. The average of O1 and O2 was indicative of what was going on at O1 and O2 individually and gave a clear overall picture. T-tests were done on the resultant traces to examine if the 13 traces (one for each of the 13 subjects) were significantly different from zero. For the ON response, it was obvious that there would be significant values as there was a large response to stimulus onset at each frequency. The 13 traces would be different from zero reflecting this response. Additional information could be gained by comparing the time points of significant t-values between frequencies. OFF responses were also examined to assess changes over frequencies.

T-tests on Difference Waves

In an attempt to better capture the changes in the ON and OFF responses, t-tests were also done on difference waves. That is, for each subject, "difference" waves were calculated by subtracting their 1.5Hz data from their 4Hz data and 13Hz data and subtracting the 4Hz data from the 13Hz data. Again, it was the average of O1 and O2 that was used for each subject. Individual subjects often differ in their responses and this allowed a subject's own response at one frequency to be compared to their response at another frequency. T-tests were done on the 13 resultant "difference" waves comparing

them against zero. If the EEG at different frequencies differed in their characteristics, the "difference" wave would detect the discrepancy.

ii) On Response

Figure 5 - Visual ON Grand Average (n=13)

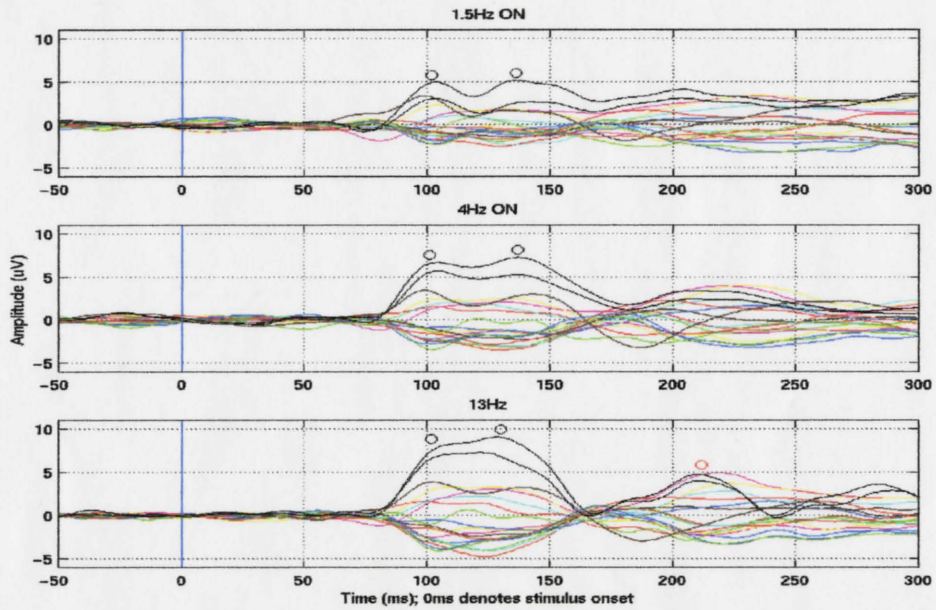
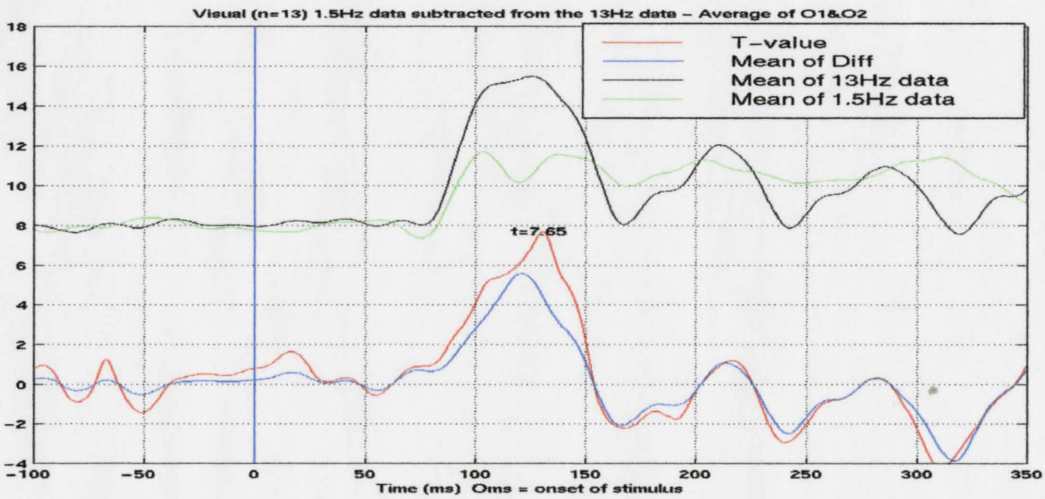


Figure 5 shows the visual ON response. All electrodes are plotted, with the occipital leads plotted in black. The vertical line at 0ms denotes stimulus onset. The visual ON had an initial negative potential (N1) at 70ms, which is hard to detect but can be seen in the occipital leads at 1.5Hz. A large positive complex followed the N1 at approximately 100ms and it became more latent and changed its morphology as frequency increased. The change in morphology can be seen by looking at the positive peaks marked by black circles in Figure 5. The 1.5Hz complex was composed of two positive peaks, but the second peak was less prominent at 4Hz and by 13Hz, it tended to

blend with first positive peak. This overall positive complex got larger with frequency increase, and reached a maximum of over 9uV at 13Hz. As well, the ON response became more dipolar as the frequency was increased from 1.5Hz to 13Hz. The first two positive peaks (P1 and P2) were followed by a third positive going wave around 210ms (P3), and was most defined at 13Hz, shown by a red circle in Figure 5. At 13Hz, this component could be due to, or at least influenced by, the presentation of more stimuli. However, it still seemed reasonable to include this component in a description of the visual ON response because this positive peak could be seen at 1.5Hz and 4.0Hz where no other stimuli had occurred yet.

Figure 6 – 13Hz-1.5Hz Difference Wave Comparison



The "difference" wave comparisons supported what was said above. The 1.5Hz subtracted from the 13Hz comparison is shown as an example in Figure 6. The vertical line denotes stimulus onset (0ms). The green trace was the mean of the 1.5Hz data while the black trace was the mean of the 13Hz data. The mean of the difference between the

two traces (the average of O1 and O2 for each subject; one frequency subtracted from another) is plotted in blue and the t-values in red. Again, recall that t-tests were done comparing the 13 traces (one for each of the 13 subjects) against zero. The point is emphasized that the ON response became larger when higher flash frequencies were seen. The largest t-value ($t=7.65, p<0.001$), at 130ms, picked up on the fact that the first complex went from being two positive peaks at 1.5Hz to one larger, blended positive peak at 13Hz.

iii) OFF Response

When t-tests were run across the OFF area, several areas of interest (peaks in the plot of t-values) emerged. They occurred at approximately: 50ms, 150ms and 240ms, 300ms and 400ms after the first omitted stimulus (6000ms in Figure 4). When comparing these points to the grand average plot of various electrode traces (Figure 4), the first point appeared to be the steady state response running into the off period. The later time points seemed to capture the true OFF complex.

Figures 7, 8 and 9 will allow a discussion at each frequency. Each figure will involve two plots. On the left, the actual data for the OFF response will be shown. All electrodes are plotted, with the occipital leads shown in black. On the right, the results from the t-test analysis of the occipital electrodes ((O1+O2)/2) will be presented. The mean of the 13 traces (the average of O1 and O2 for each subject) will be plotted in blue and the t-values in red. T-tests were done comparing the 13 traces against zero. Any value with a $p<0.01$ will be considered significant; this requires a t-value that is greater

than 3.055. The vertical line denotes the first omitted stimulus. This is occurring at 6000ms (with respect to the onset of the stimulus).

Figure 7 – 1.5Hz OFF Data Analysis

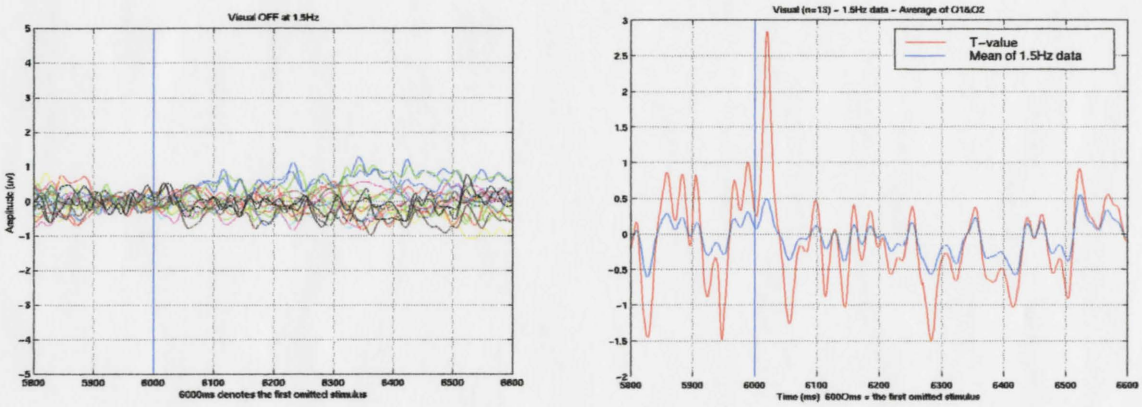


Figure 7 shows the off period at 1.5Hz. As no significant t-values occurred, what the raw data showed was confirmed: the activity after the first omitted stimulus presented no patterned response that could be labelled an OFF response.

Figure 8 – 4Hz OFF Data Analysis

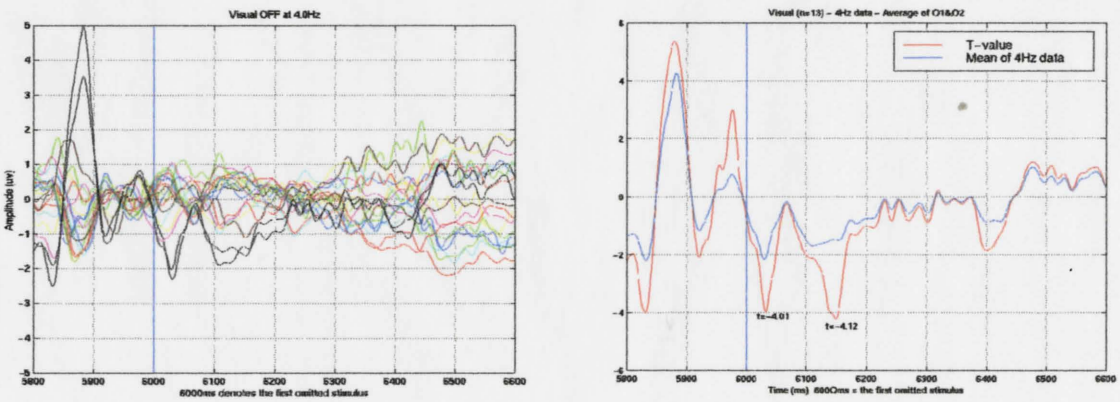
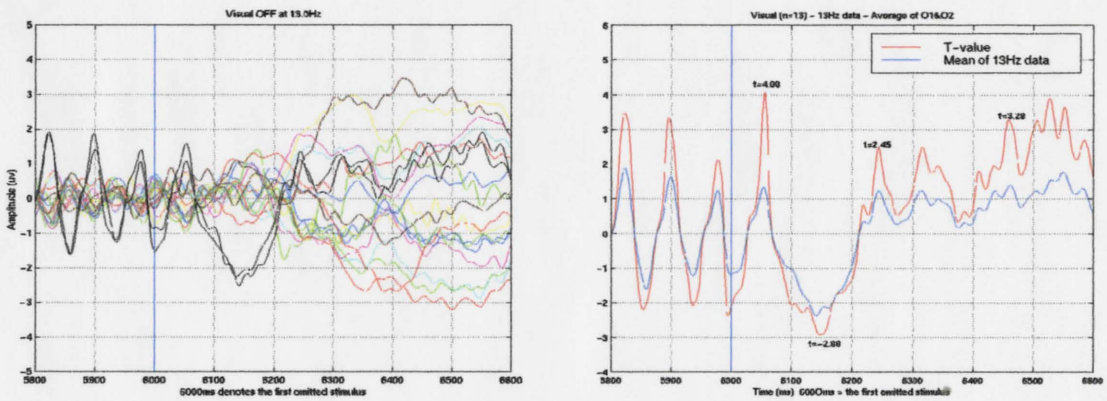


Figure 8 shows the off period at 4Hz. The 4Hz data gave significant t-values of –4.01 ($p<0.01$) and –4.12 ($p<0.01$) at 30ms and 150ms respectively. The negative peak at 30ms (after the first omitted stimulus) looked similar to the negative peak that occurred before the large positive peak in each steady state event and may be more associated with the steady state response rather than the OFF. The second time point appeared to be associated with the actual OFF response (and not the steady-state response running into the OFF). Since this same area was not significantly different from zero in the 1.5Hz data, the 150ms negative peak of the OFF seemed to increase as frequency increased from 1.5Hz to 4Hz.

Figure 9 – 13Hz OFF Data Analysis



At 13Hz, Figure 9, the following significant or near significant values were seen: 4.08 ($p<0.01$) at 50ms; -2.88 ($p<0.05$) at 150ms; 2.45 ($p<0.05$) at 245ms; and 3.28 ($p<0.01$) at 450ms. The 150ms area indicated activity again, as in the 4Hz data (though the value is not as significant as in the 4Hz data). Something happened at this point for

the 4Hz and 13Hz stimulation but not for the 1.5Hz. The 250ms and 450ms t-values indicated that late components of the OFF changed with frequency increase. The other two frequencies did not show values near significance in these areas.

In an attempt to better capture the changes in the OFF response, the "difference" wave comparisons were done again and the results are presented in Figures 10, 11 and 12. Recall that for each subject, a "difference" wave was calculated by subtracting their 1.5Hz data from their 4Hz data and 13Hz data and subtracting the 4Hz data from the 13Hz data. The average of O1 and O2 was calculated for each subject in order to make the comparison. The vertical line at 6000ms represents the first omitted stimulus. All time points in describing different components of the OFF are with respect to the first omitted stimulus.

Figure 10 - 4-1.5Hz Difference Wave Comparison

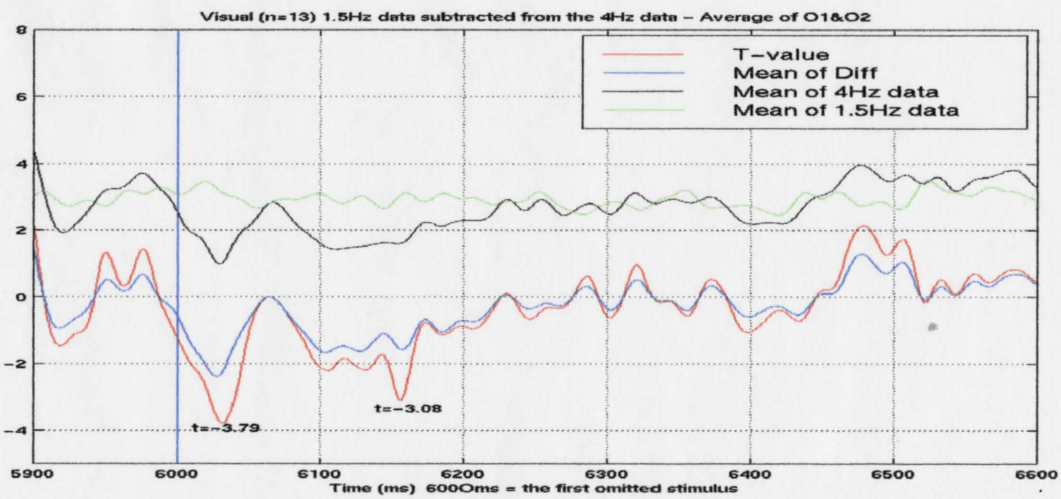
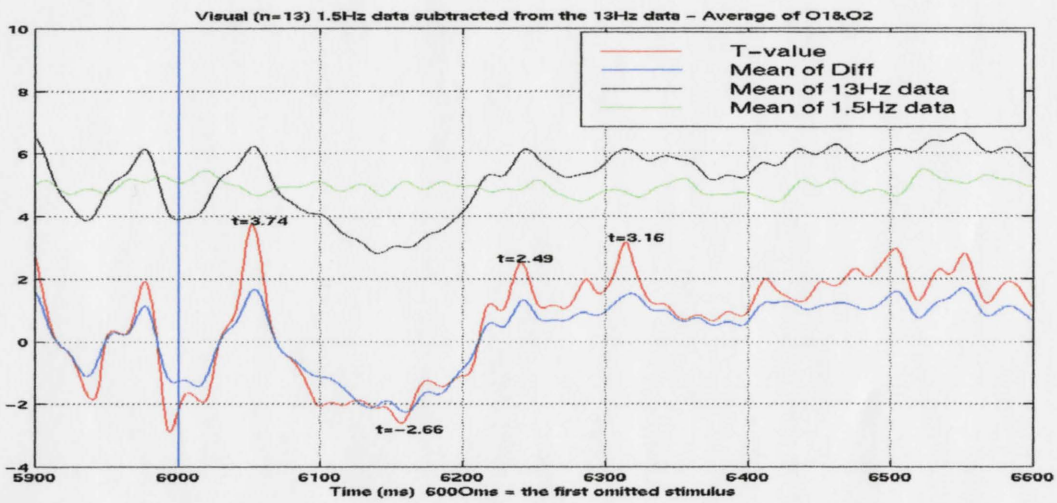


Figure 10 shows that when the 1.5Hz data were subtracted from the 4Hz data, two areas of significance emerged: 31ms ($t=-3.79, p<0.01$) and 155ms ($t=-3.08, p<0.01$). The

t-value at 155ms meant that the first major component of the OFF became more negative as frequency was increased.

Figure 11 - 13-1.5Hz Difference Wave Comparison



Four peaks are prominent in the plot of t-values of Figure 11, when the 1.5Hz data are subtracted from the 13Hz data: 50ms ($t=3.74, p<0.01$), 157ms ($t=-2.66$, $p<0.05$), 240ms ($t= 2.49$, $p<0.05$) and 312ms ($t=3.16, p<0.01$). The t-value for the 150ms area was greater in the 4Hz-1.5Hz comparison, suggesting that the change in that component of the OFF was more sensitive to the difference in going from 1.5Hz to 4Hz than 1.5Hz to 13Hz. The change in the positive going component (~300ms) did not show up clearly in the previous comparison but does so here.

Figure 12 - 13-4Hz Difference Wave Comparison

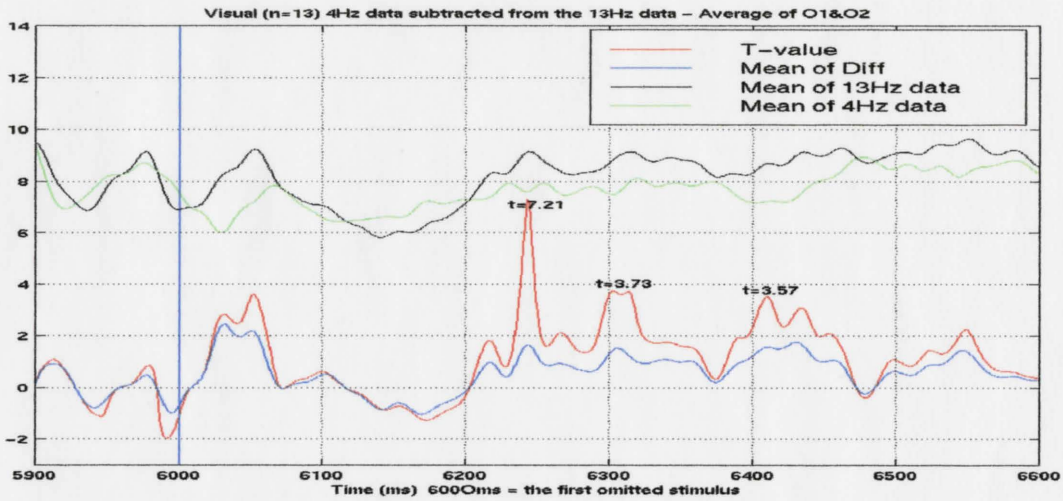


Figure 12 compares 4Hz and 13Hz and shows that no significant t-value occurred at 150ms. Significant values occurred at 50ms ($t=3.60, p<0.01$), 243ms ($t=7.21, p<0.001$), 300ms ($t=3.73, p<0.01$) and 408ms ($t=3.57, p<0.01$). Note that the 50ms peak is not labelled in Figure 12 whereas the other three peaks are labelled. The second seemed to be picking up on another positive component that occurred at 13Hz but not necessarily at the other frequencies. The 300ms peak became more positive with the higher frequency of stimulation. The 400ms negative peak seemed to become less negative as frequency was increased although this was only significant in the 13-4Hz condition. It did not show significance in the 13-1.5Hz condition and the situation may actually be reversed (4Hz is more negative than 1.5Hz) in the 4-1.5Hz condition.

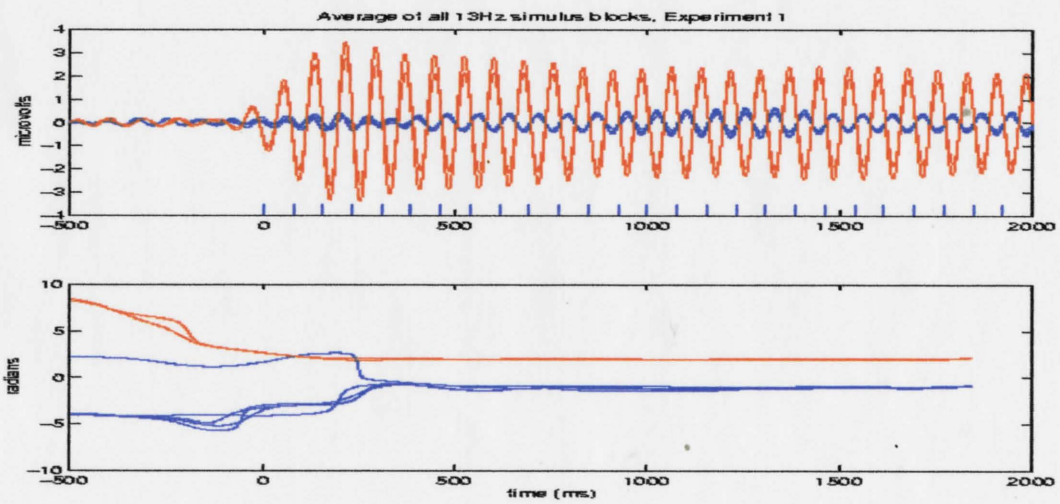
To summarize, the OFF response had three main components: a negative peak at 150ms, a positive going wave between 245 and 300ms and a negative peak around 400ms. Figures 8 and 9 showed that the most consistent change in the OFF response was seen at 150ms (after the first omitted stimulus). The negative peak at this time point

increased as the repetition rate was increased. The difference wave comparisons confirmed this finding.

iv) Steady State Response

The discussion thus far has focussed on transient responses, but the visual data also provided a clear steady state response as can be seen in Figure 13 below. In order to look at the 13Hz steady state response, the data were filtered with a 10-16Hz finite impulse response (FIR) filter. The upper plot shows the occipital electrodes (O1 and O2) in red and the frontal electrodes (F7, F3, Fz, F4, and F8) in blue. The occipital leads gave a large response (approximately 7uV from peak to trough) and lined up immediately with each other at the onset of the stimulus. The frontal leads stabilized at 180degrees with respect to the occipital leads. It took about 5 pulses for this to occur. The lower plot of Figure 12 gives the phase of each electrode plotted above. Calculation of phase was done with a Hamming window 2 steady state pulses wide and shifted at 1ms time steps. Electrodes that are 2pi apart are actually in phase with each other.

Figure 13 – Visual Steady State Response



C) AUDITORY DATA

i) On Response

Figure 14 – Auditory ON Response (n=10)

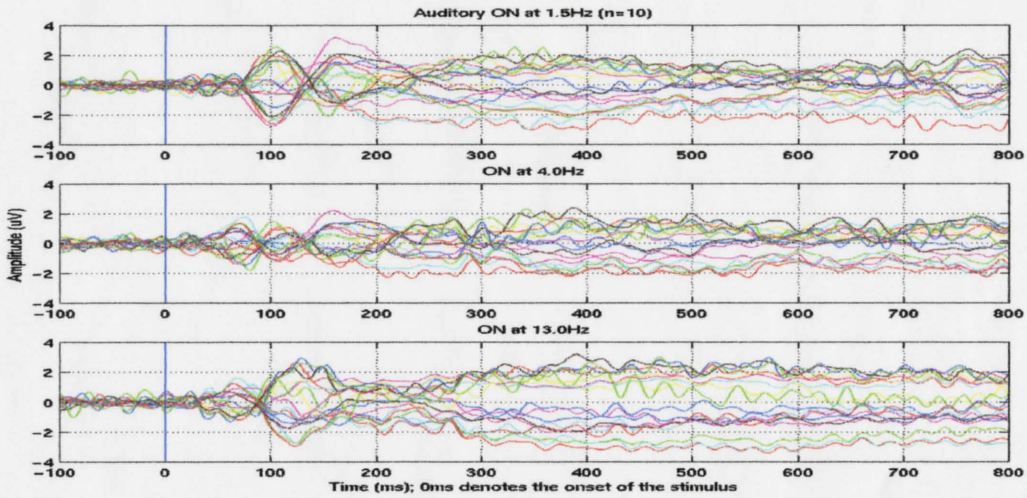
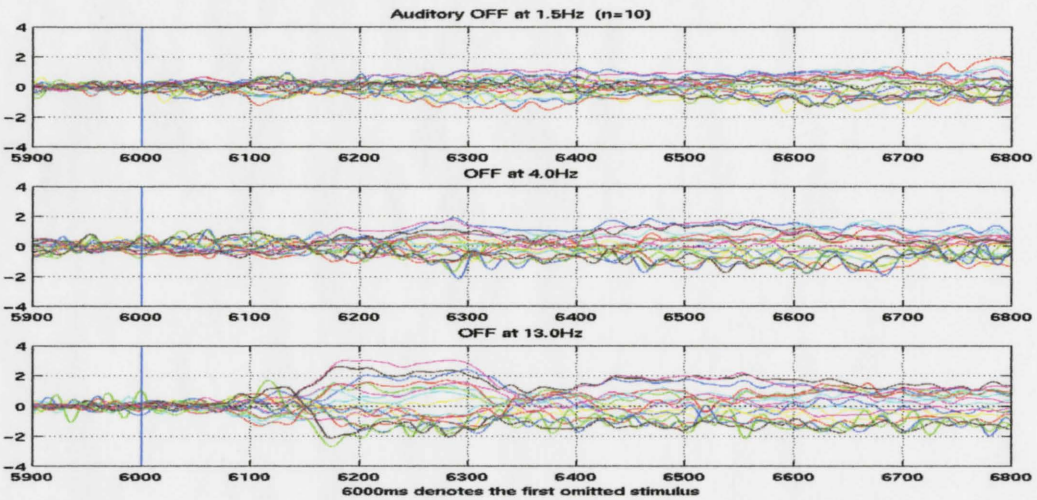


Figure 14 shows the auditory ON response. All electrodes are plotted. The data were common referenced and filtered with a low pass filter set at 50Hz.. At 1.5Hz, the auditory ON was prominent and dipolar at 100ms. Unlike the visual ON, the auditory ON did not seem to maintain the same general characteristics across frequency. The smallest response occurred at 4Hz and it appeared very dissimilar to the other two frequencies. A dipolar complex seemed to be there at 100ms but was accompanied by dipolar complexes on either side. The 13Hz ON reached approximately the same amplitude as the 1.5Hz response, but it was spread out over a longer interval. As well, its latency was longer with the peak response at 125ms after stimulus onset. This component was preceded by a small 70ms, dipolar response, which can be seen at each repetition rate.

ii) OFF Response

Figure 15 - Auditory OFF Response (n=10)



The auditory OFF response is shown in Figure 15. As was the case for the visual data, an OFF response seemed to develop as frequency of stimulation was increased. Very little change in the responding occurred after the first omitted stimulus for the 1.5Hz data. It was hard to discern if anything was happening in the OFF area of the 4Hz data as well. There seemed to be a long positive going waveform beginning at about 200ms. Yet, there was no doubt that there was a 13Hz auditory OFF response. The OFF at 13Hz consisted of two main components: a small dipolar response (about 3uv) spanning 80-150ms; and a larger dipolar response (about 5.5uv) spanning 150-350ms.

iii) Looking at Cz only

Figure 16 - Auditory ON and OFF Responses at Cz

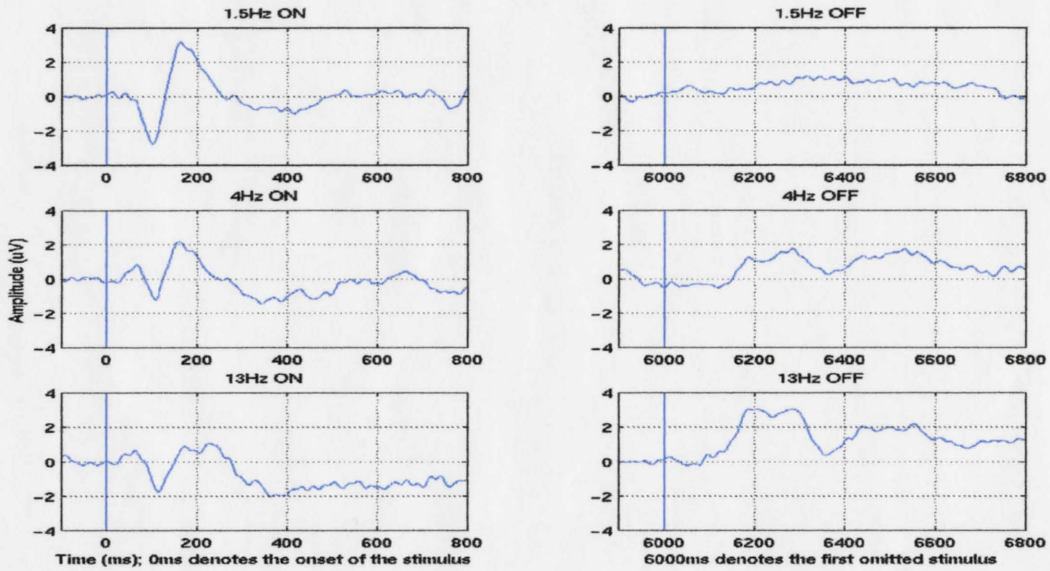


Figure 16 plots the ON and OFF responses for Cz only. The data were again common referenced. Figure 16 is an attempt to give a better description of the auditory responses. The ON response, shown in the left column, did seem to maintain the same characteristics, a negative peak at 105ms (N1) and a positive peak (P2) at 170ms, across frequency when looking at Cz. The P1 component, that precedes the N1, showed up at 4Hz and 13Hz. The ON response, as measured by the N1-P2 amplitude, decreased as frequency was increased. The N1-P2 amplitude went from 5.7uV at 1.5Hz to 3.2uV and 2.5uV at 4Hz and 13Hz respectively. The OFF response, shown in the right panel of Figure 16, is more easily described by focusing on the Cz plot rather than the plot of all electrodes as was shown in Figure 15. At 13Hz, the OFF was comprised of three components: two positive peaks, at 185ms (P1off) and 285ms (P2off), and a negative

peak at 350ms (N1off). The OFF, as was determined from the plot of all electrodes, developed with frequency increase. There was still little activity in the OFF area of the 1.5Hz data. The 4Hz OFF response, now detectable in the Cz trace, showed the three OFF components. All three peaks were most pronounced at 13Hz.

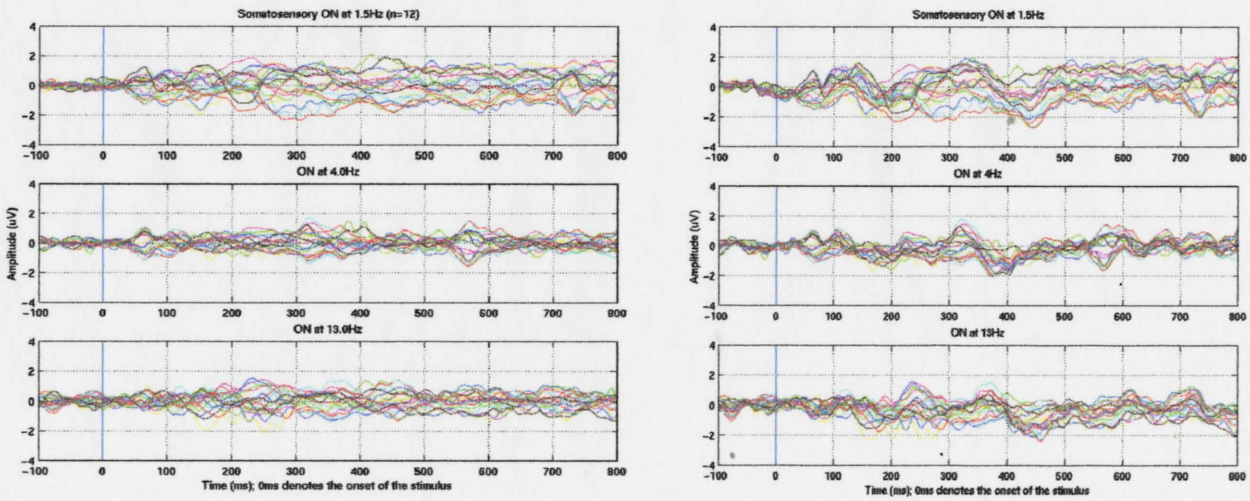
D) SOMATOSENSORY DATA

As was mentioned previously, the responses were least clear in the somatosensory data. As a consequence, it was very hard to discuss the somatosensory responses. For the common referenced data, responses were often barely detectable. The situation for the ear-referenced data was better. As a result, though it has been the practice to present data with a common reference, the ear-referenced data will also be presented for the somatosensory system.

i) ON Response

Figure 17 - Somatosensory ON Response (n=12)

a) Common Reference **b) Ear Reference**

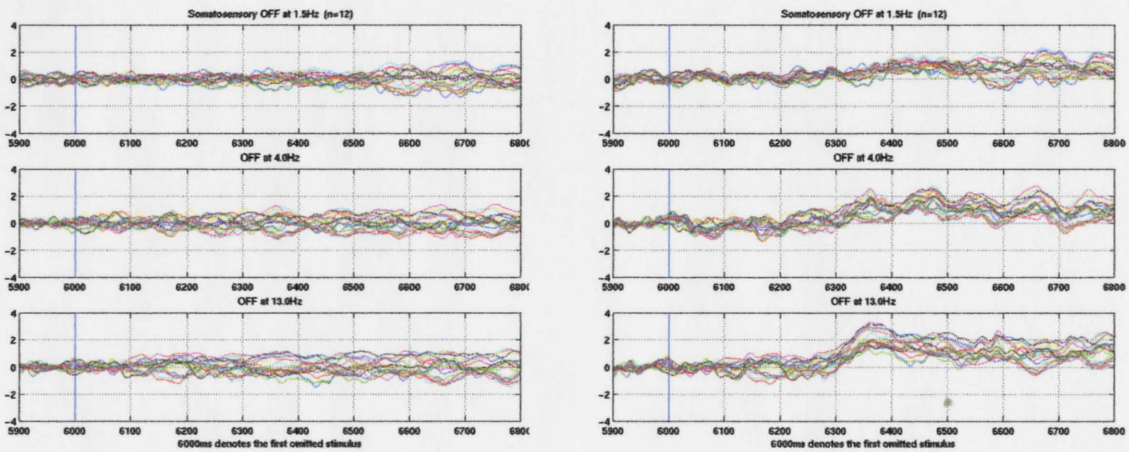


The ON response for the common referenced data, presented in Figure 17a, was not obvious. There was a small dipolar response being elicited at 70ms by the 1.5Hz and 4Hz stimulation. This response appears to be attenuated in the 13Hz data. The ear-referenced data is presented in Figure 17b. The 1.5Hz and 4.0Hz traces had an early, dipolar response between 50ms and 60ms. This was consistent with the ON response described by Bernhard Baier in his undergraduate thesis examining somatosensory ON and OFF responses to 40Hz stimulation generated by the same stimulator used here.

ii) OFF Response

Figure 18 - Somatosensory OFF Response (n=12)

a) Common Reference **b) Ear Reference**



The OFF response is shown in Figure 18. It was very difficult to see any somatosensory OFF response when the data were given a common reference, see Figure 18a. However, a discussion can be had around the data created with an ear-reference, Figure 18b. As with the other two modalities, the somatosensory OFF response increased

as frequency was increased. The somatosensory OFF was best characterized as a slow positivity that became more pronounced as frequency was increased. The OFF response in this modality was quite latent compared to that seen in the visual and auditory domains. The greatest activity occurred at about 350ms. At 13Hz, the positivity peaked 365ms after the first omitted stimulus with an amplitude of 3uV.

iii) Looking at Cz only

Figure 19 – Somatosensory ON and OFF Responses at Cz

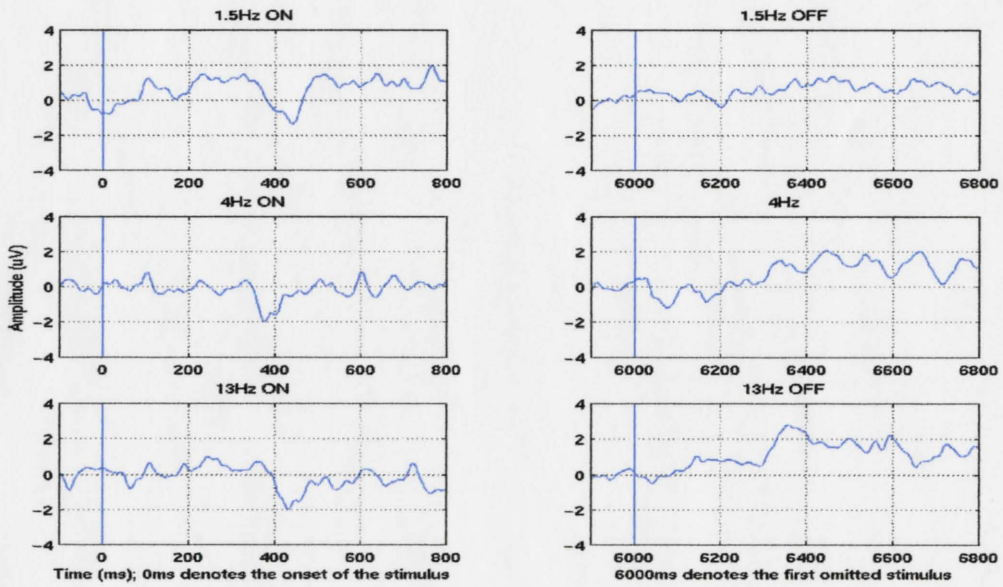


Figure 19 is an attempt to give a better description of the ON and OFF responses in the somatosensory data. The plot is of Cz, the reference electrode, only. It is the ear referenced data presented in Figure 19. The most prominent ON response, shown in the left column, was a late negative peak. The latency differed across frequency: 439ms, 374ms, and 430ms for 1.5Hz, 4.0Hz and 13.0Hz respectively. Components occurring

this late were hard to interpret, especially in the 13Hz data, because other pulses had been experienced. The OFF response, shown in the right column of Figure 19, was a positive peak at 355ms after the first omitted stimulus. This peak was most obvious in the 13Hz plot. Again, the OFF developed as frequency was increased.

DISCUSSION

Effect of repetition rate on the visual ON response

The visual ON response consisted of four components: N1 (70ms), P1 (100ms), P2 (140ms) and P3 (210ms), Figure 5. Though the N1 and P3 showed little change, the other two components (P1 and P2) were greatly increased in amplitude at 13Hz, where the two peaks blended into one. As well, the response in the 100-150ms range became more dipolar as the frequency was increased from 1.5Hz to 13Hz. Overall, P1 and P2 became significantly larger as repetition rate was increased. The difference wave analysis was presented (Figure 6) which showed a significant increase when 13Hz was compared to 1.5Hz. It should be noted that the 4Hz to 1.5Hz comparison was also significant and therefore, the enhancement of the 13Hz ON response cannot be attributed to the fact that a second stimulus was received 78ms into the stimulus train.

Effect of repetition rate on the visual OFF response

To examine omitted stimulus potentials (OSPs) in the visual system, Bullock et al. (1994) presented human subjects with a range of flash frequencies between 0.3Hz to 40Hz. The frequencies above 2Hz were classed as the "high" range and those below 2Hz as the "low" range (p.43). The OSPs either followed the end of a train of stimulation or were single omissions within the train. The resultant OSP was reportedly the same in either case with the slight difference in morphology of the OSP to a single omission attributed to the superimposition of the response to the next event. If this interpretation is

accepted, the results can be compared to the end of train OFF responses reported here. The most striking result that Bullock et al. documented was that though OSPs were found below 2Hz and above 5Hz, no OSP was found between 2Hz and 5Hz. In fact, they classified 2 different OSPs, the "fast OSP" (>2Hz) and the "slow OSP" (<2Hz). The three repetition rates (1.5Hz, 4Hz and 13Hz) in this experiment span the three areas reported to produce different OFF responses.

The "fast OSP" had two main peaks: a negative peak 120ms after the first omitted stimulus and a positive peak between 170-230ms after the first omitted stimulus. The visual data in Experiment One support this finding. The 1.5Hz stimulation produced no OFF response after 6 seconds of stimulation. The occipital leads at 4Hz and 13Hz data showed a negative going OFF response 150ms after the first omitted stimulus followed by a positive peak between 245ms and 300ms. In addition, the 4Hz and 13Hz OFF responses included a longer latency negative component around 400ms (Figure 4) that was not reported by the Bullock group. Note that the 4Hz data evoked an OFF response quite similar to the 13Hz OFF response whereas Bullock reported no OFF response in the 2-5Hz range. The "slow OSP", a slow positive wave occurring 500 to 1100ms after the first omitted stimulus, was not replicated here, although we did not probe repetition rates as low as Bullock did. As was indicated above, the 1.5Hz data (which falls in the <2Hz range that is supposed to produce the slow OSP) had no detectable OFF response activity in the 2-second gap following the end of the train.

Though the main component (150ms) of the OFF response did not differ between 4Hz and 13Hz, it tended to be larger (i.e. more negative) at 13Hz. When comparing the

4Hz and 13Hz to the 1.5Hz data at the corresponding time point, a significant (4Hz) or near significant (13Hz) value was found. The peak was becoming more negative as repetition rate increased. The later components of the OFF response (positive peak between 245ms and 300ms; negative peak around 400ms) were larger in the 13Hz condition when comparing them to either of the other two frequencies. The comparison was significant for both components at 4Hz and for the positive component at 1.5Hz. Overall, the OFF response seemed to develop as repetition rate was increased. Bullock's claim that the OSP was not continuous as frequency was increased contrasts the results discussed here for the range 4Hz to 13Hz.

There are several possibilities for explaining the discrepancies between the Experiment One data and Bullock's work. The differences in the later OFF components are probably attributable to differences in stimulus procedure. Experiment One involved gaps between trains of a fixed duration (2 seconds). Bullock et al.'s subjects experienced gaps consisting of single as well as multiple omitted stimuli which may not have allowed the later components of the OFF response to be seen at high stimulus repetition rates.

The presence of an OFF response at 4Hz in this data but not in Bullock et al.'s data could be the result of other experimental differences. It is not made clear how much stimulation the subjects received in the Bullock et al. experiment. For example, the Bullock et al.'s train paradigms used 2-30 sec trains following 2-30sec rest periods. This seems to imply that the subject only experienced two trains of stimulation at each frequency. The present experiment gave the subject 120 trains of 6-second stimulation at each frequency. Perhaps more stimulation was required for the subject to develop a

representation of the stimuli at certain repetition rates. The 4Hz stimulation only delivered 24 stimuli per train, but experiencing the train 120 times may have allowed enough experience to accumulate to produce an OFF response. As well, Bullock specified different types of attention were required to get good slow and fast OSPs. Slow OSPs required attention but not fixation and fast OSPs required fixation but not attention. It did not say what method was attempted in the 2-5Hz range. This study had the subject try and maintain focus on a spot on the bristol board that surrounded the LED while counting the OFF times for all frequencies. Therefore, fixation and attention were both maintained. This could account for differences in the responses.

Effect of repetition rate on the auditory ON response

The ON and OFF responses in the auditory domain were also dependent on repetition rate. The plot of all electrodes (Figure 14) showed that the general characteristics of the ON were different across frequencies. A dipolar potential occurred around 70ms. Its amplitude varied with repetition rate. Another dipolar complex followed and it differed in size and latency across repetition rate. The ON response that was seen in Figure 16, where Cz only is plotted, displayed the components (P1, N1, P2) that have long been reported to auditory stimulation (Pfefferbaum et al., 1971, Davis et al., 1972, Hillyard & Picton, 1978). The ON response did not increase as frequency was increased, as was the case in the visual data. In fact, the N1-P2 amplitude decreased as repetition rate was increased. There is the possibility that this effect may have been generated by the difference in off times. Pfefferbaum et al. (1971) reported that an

increase in the duration of the interval that precedes the ON or OFF response leads to an increase in that response. A longer off interval should, therefore, lead to a larger ON response. The length of the pause between stimulus trains in Experiment One was timed with respect to the first omitted stimulus and hence, was different for the different repetition rates. The off periods had lengths of 2.656s, 2.240s and 2.067s for 1.5Hz, 4Hz and 13Hz respectively. Consistent with the finding of Pfefferbaum et al. (1971), the 13Hz stimulation, which had the shortest off interval, elicited the smallest ON response. However, Pfefferbaum et al. compared two intervals that differed greatly; the long interval was 2500ms and the short interval was 500ms. The pause lengths in this experiment differ only slightly. Overall, characteristics of the ON response seem to depend on repetition rate.

Effect of repetition rate on the auditory OFF response

The auditory OFF response seemed to develop with repetition rate. The OFF response at Cz (Figure 16) had three components: P1 (185ms), P2 (285ms) and N1 (350ms). These components were all largest at 13Hz. Note that as in the visual case, a very late negative component occurred. As the literature reports (Shweitzer & Tepas, 1974), the morphology of the OFF response corresponds to the morphology of the ON response. Though the N1-P2 complex is not prominent, it can be seen in the OFF response in the frontal leads.

Effect of repetition rate on the somatosensory ON response

The common referenced data showed a dipolar ON response around 50ms that was small and did not differ between repetition rates. The 50ms response is consistent with the ON response to 40Hz stimulation reported by Bernhard Baier in his undergraduate thesis. The ON response at Cz (Figure 19) in the ear-referenced data was a very latent negative peak (~400ms). All frequencies showed this response. The interpretation of a component at 400ms is difficult because other pulses have been received. Overall, repetition rate does not seem to effect the ON response in the somatosensory domain.

Effect of repetition rate on the somatosensory OFF response

The ear-referenced data show that the somatosensory OFF response increased as repetition rate was increased. The OFF was a slow, positive wave that peaked around 350ms. Again, as in the visual and auditory modalities, a late OFF component was present and most prominent at 13Hz. The polarity of the late component differed between modalities. Since all experimental manipulations (number of presentations, counting the gaps etc.) were held constant, this component must relate to differences in sensory processing.

CHAPTER THREE

EXPERIMENT TWO

Experiment One showed that the ON response increased over repetition rates and that the OFF response appeared at 13Hz but not at 1.5Hz. Were these increases due to the fact that more stimulation (more pulses per train) was received at 13Hz? Or, was this a function of the rate of stimulation? Experiment Two addressed these questions. As well, the following question was examined: do highly dynamic forms of plasticity contribute to the development of representations of simple stimuli in primary cortices?

Experiment Two sought to equate the amount of stimulation seen at 1.5Hz and 13Hz in order to answer the above questions. There were two ways to do this: increase the 1.5Hz trains from 9 stimuli to 78 stimuli (the number of pulses experienced during 6 seconds of 13Hz stimulation in Experiment One) or reduce the 13Hz trains to 9 stimuli. The latter was more efficient. If experience was a significant variable, the ON and OFF responses, originally small, should increase as the subjects gained experience over trials. However, if robust ON and OFF responses are seen immediately, repetition rate may have been the more important variable in Experiment One. Of course, the answer could also fall in between these two extremes. ON and OFF responses might be detectable initially but change as more exposures were delivered.

METHODS

Subjects

The subjects were 36 undergraduate and graduate students, 24 females and 12 males, from McMaster University. Subjects received either a monetary reward or course credit for their participation. The age of the subjects ranged from 18 to 47 years of age.

Materials

The materials used were identical to that described for Experiment One, with only visual stimulation implemented in this experiment. That is, subjects wore electrode caps with an array of Sn electrodes that were in keeping with the international 10-20 system. As well, ear electrodes were used for recording. The reference electrode was Cz and the ground was at a site between Cz and Fz. The skin below each electrode site was abraded and the electrode cavity was filled with Electro-Gel to lower the impedances below 5 ohms. The data were collected with a 32 channel Synamps EEG (NeuroScan Inc.). The recording was continuous with a sampling rate of 1000Hz. The filter for data acquisition was set at DC to 200Hz. Again, the visual stimulation was provided by the LED described for Experiment One. As described below, both 13Hz and 14Hz stimulation was utilized.

Procedure

The purpose of Experiment Two was to analyze the effect of experience on the ON, OFF and steady state responses. The visual domain provided the best signal to noise ratio and hence, this experiment used visual stimulation only. As well, only one frequency of stimulation was presented within subject. There were three groups in

Experiment Two: Replication One (n=12), Replication Two (n=24) and Return Subjects (n=10). Replication One involved 13Hz stimulation and Replication Two involved 14Hz stimulation. The Return Subjects were a subset of the Replication Two Subjects. That is, 10 of the 24 Replication Two subjects returned 24 hours after the original session for a second session. The Return Subjects experienced 14Hz stimulation in the exact same procedure on both days. The Return Subjects were an attempt to measure retention effects.

Subjects were situated as in Experiment One: seated in a dimly lit room in a high back chair with the LED approximately one meter away. They were instructed: to remain still, blink as infrequently as possible and keep their eyes open for the duration of the experiment. White noise was delivered through headphones. Once the recording began, the session lasted about 50 minutes.

Experiment Two contained seven blocks of stimulation. Blocks were one of two types: "test" blocks or "training" blocks. Though the frequency of stimulation remained constant, the length of the train differed between block types. "Test" blocks were comprised of trains of very short duration. Only 9 pulses of visual steady-state stimulation were delivered per train, resulting in 615ms and 571ms trains of stimulation for Replication One and Replication Two respectively. Each train was followed by a 2 second off period timed from the first omitted stimulus. Note that 9 pulses were equivalent to the number of pulses seen at 1.5Hz in Experiment One. "Training" blocks consisted of trains with 78 pulses (6seconds) followed by a 2 second off, timed from the first omitted stimulus. These trains were identical to those in Experiment One. "Test"

blocks had 100 trains of stimulation and "training" blocks had 60 trains. Again, to control attention, subjects were counting the off periods during each block and reporting number to the experimenter. The number of counts reported by each subject for each block can be found in Appendix III. The subjects were accurate in their reports and therefore there is confidence that the subjects paid attention to the stimulation. The order of presentation of blocks was as follows: initial "test" block; 2 "training" blocks; second "test" block; 2 "training" blocks; final "test" block. "Test" blocks will always be referred to as "Test Block 1, 2 or 3", with "Test" Block 1" being the first experienced and "Test Block 3" being the last. The subject's EEG was recorded continuously throughout the session.

Signal Analysis

Each subject's data were analyzed by creating a 1500ms epoch for each block of stimulation. For the "test" blocks, this epoch covered 500ms before stimulus onset, the entire stimulus period (692ms from onset to first omitted stimulus for Replication One; 642ms for Replication Two) and part of the 2second off period (808ms from the first omitted stimulus for Replication One; 858ms for Replication Two). For the "training" blocks, this epoch covered 500ms before stimulus onset and then 1500ms into the 6-second stimulus period. Artifact rejection, set at -100uV to +100Uv, was based on the Fp1 and Fp2 electrodes. All data were linearly detrended, given a common reference and re-baselined to the 500ms period before stimulus onset. The filtering was determined by the type of response being investigated (ON versus OFF response; transient versus steady state response) and will be reported where necessary.

"Difference" wave analysis

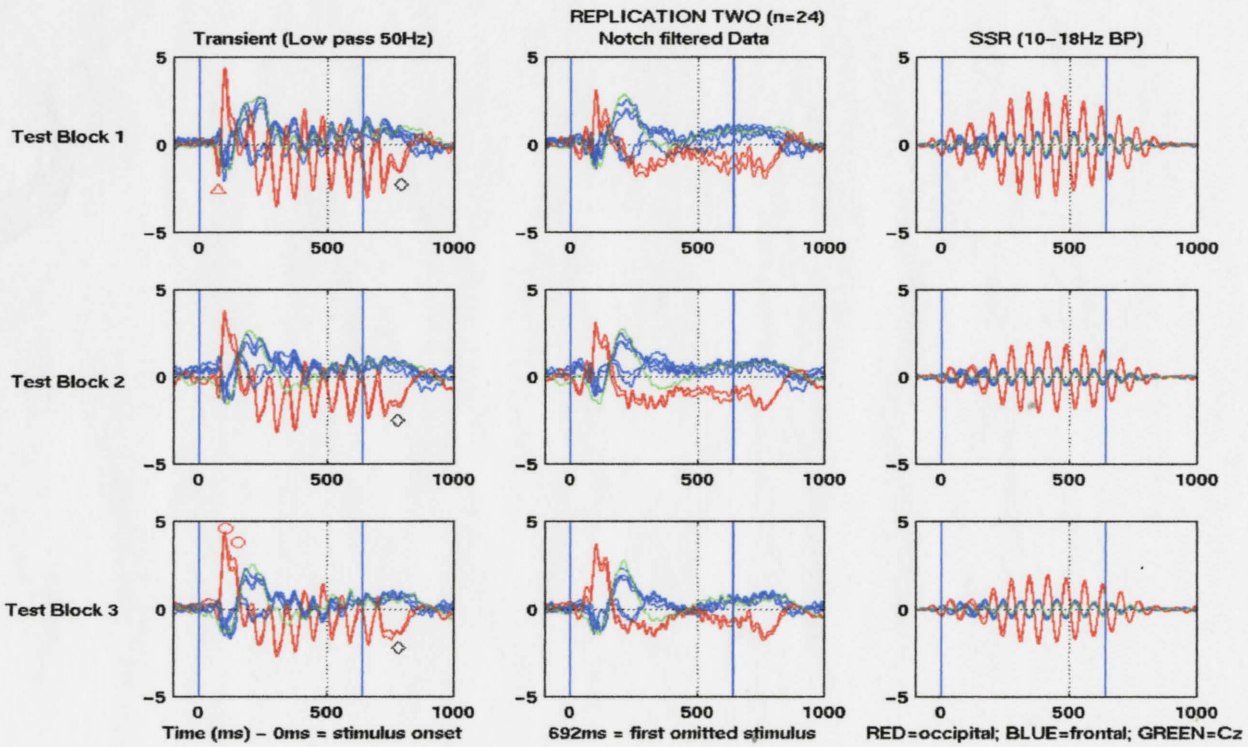
The "difference" wave analysis was trying to track systematic changes that may have occurred. The changes looked at occur over time and hence, experience. These two things could not be separated. As in Experiment One, a "difference" wave analysis was conducted. For each subject, the average of O1&O2 was calculated for each "test" block. "Difference" waves were then computed by subtracting one "test" block from another, within subjects. This gave one "difference" wave per subject per comparison. T-tests were done on the resultant "difference" waves comparing them against zero, for the group as a whole, n=12 (Replication One) or n=24 (Replication Two). If changes were occurring across test blocks, this would be reflected by significant t-values at the point of change. The difference would have to show up in most subjects for the t-value to be significant. Replication One involved 12 subjects and a t-value of 3.106 or greater ($p<0.01$) was considered significant. Replication Two involved 24 subjects and a t-value of 2.807 or greater ($p<0.01$) was considered significant. Note that abbreviations will be used when describing the results of these comparisons. For example, the comparison where "Test Block 1" is subtracted from "Test Block 2" will be abbreviated to "TB2-TB1".

RESULTS

The results of Experiment Two were extensive. Therefore, the results, as presented here, are divided into two sections: A) Overall Picture and B) Detailed Analyses. It is the goal of the first section to present the primary findings only. Replication Two will be emphasized because it had the larger number of subjects and it is the group from which the Return Subjects were drawn. Replication One will be described briefly. The second section will give the fine details of the analyses reported in the first section.

A) OVERALL PICTURE

Figure 20 – Replication Two "Test" Blocks



The grand averages for the "test" blocks of Replication Two are presented in Figure 20. The data were common referenced, linearly detrended and baselined to the last 500ms before stimulus onset. Each row in Figure 20 represents a "test" block. Each column presents the data filtered in a different way. The left column shows the data when filtered with a low pass filter set at 50Hz ("transient"). The data in the middle column have been notch filtered ("notch"). That is, in addition to the low pass 50Hz filter, 10-18Hz has been removed, thereby removing the fundamental frequency of stimulation (14Hz). The right column shows the steady state data; the data were filtered with a 10-18Hz band pass filter ("SSR"). In each subplot, the first vertical line denotes the onset of the stimulus and the second denotes the offset of the stimulus. The red traces are the occipital leads; blue are the frontal; and green is the reference, CZ.

Figure 20 presents three of the main findings of Experiment Two. First, the low pass filtered data (and the notch filtered data) showed that the OFF response was seen right away. Short bursts of 14Hz visual stimulation resulted in an OFF response in "Test Block 1" that did not change much over the following "test" blocks. The OFF response, as described by the occipital leads, was a large negative response that peaked 140ms after the first omitted stimulus. The main peak of the OFF is indicated by a black diamond for each "test" block of the "transient" data (left column).

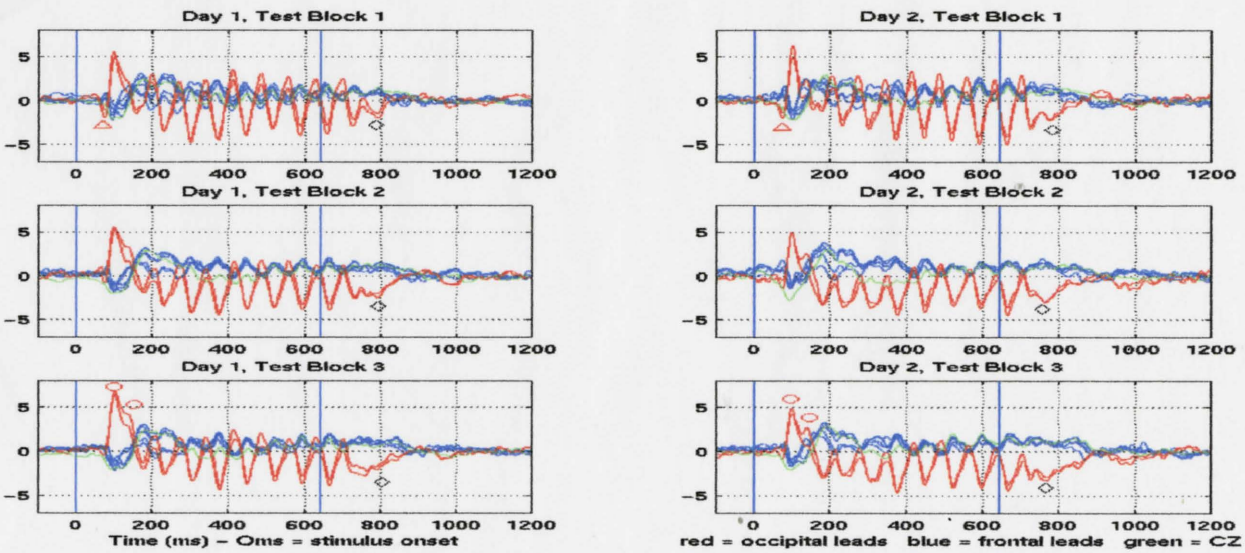
Second, Figure 20 shows that an ON response also occurred in the first "test" block, and it did change over the experiment. The ON response was characterized by three components: N1 (80ms), P1 (100ms) and P2 (125ms). The N1 component of the ON, shown by a red triangle in the upper subplot of the "transient" data, became less

negative as it went from "Test Block 1" to "Test Block 3". This change was not significant for Replication One (not shown here) but was for Replication Two. As well, the P2 component got significantly larger across "test" blocks, for both replications. The P1 component did not change for either replication. Red circles in the bottom subplot of the "transient" data in Figure 20 indicate P1 and P2.

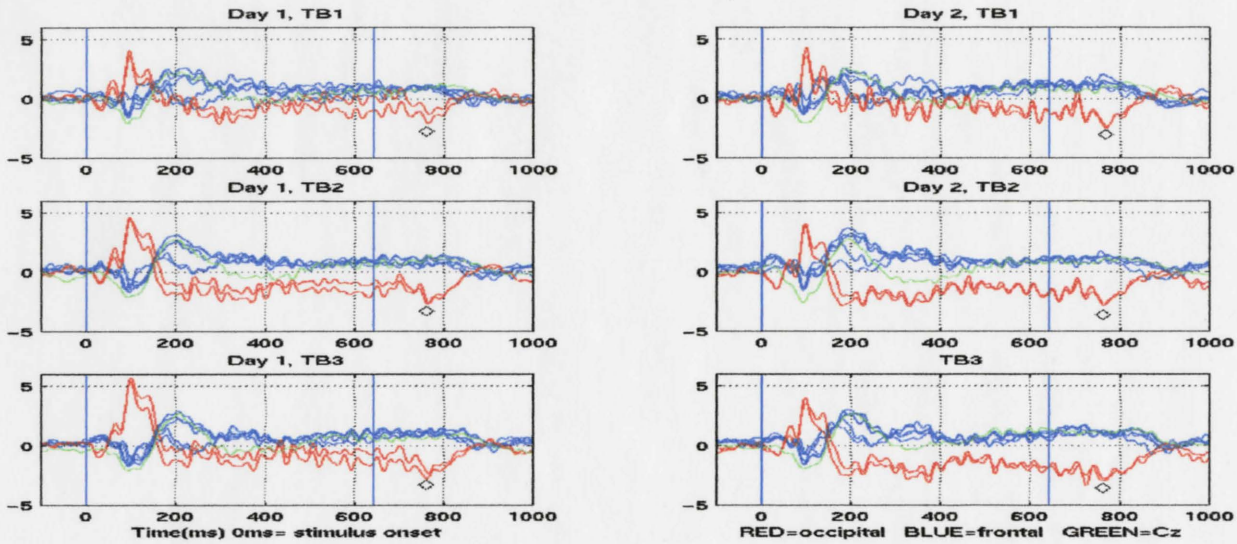
Third, the "SSR" column of Figure 20 gives a clear picture of the steady state response to the 14Hz stimulation in each "test" block. The steady state response changed over blocks in both amplitude and phase. "Test Block 1" had a larger steady state response and this response ran further into the OFF area than it did during the other "test" blocks. As well, there was a phase shift across blocks. The ninth steady state event, which is the pulse that comes directly before the second vertical line (signaling the first omitted stimulus), occurred later in each "test" block.

Figure 21 – Return Subjects "Test" Blocks

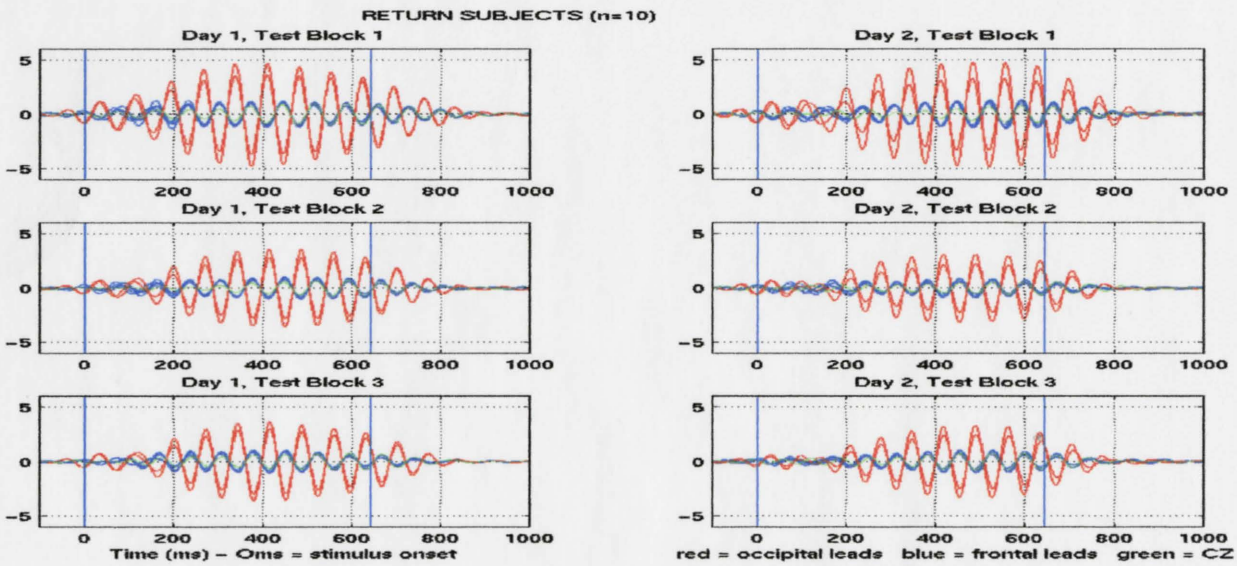
(a) Transient Response (Low pass 50Hz)



(b) Notch filtered Data



(c) SSR (10-18Hz BP)



A subset of subjects (n=10) from Replication Two, the Return Subjects, returned 24 hours after the first session to repeat the same procedure. Therefore, there are two days of results, Day 1 and Day 2, and three "test" blocks on each day. Figure 21 shows

the "test" blocks from Day 1 (left column) and Day 2 (right column). The three panels show the data filtered in the three different ways that were shown for Replication Two in Figure 20. Panel (a) presents the "transient" data; panel (b) shows the "notch" data; and panel (c) shows the "SSR" data. For further detail on the filters, refer back to the Figure 20 discussion. The first vertical line in each subplot denotes the onset of the stimulus and the second denotes the first omitted stimulus. The red traces are the occipital leads; blue are the frontal; and green is the reference, CZ.

As was seen to the "test" blocks in Replication Two, ON and OFF responses were clear with the short burst of stimulation, even after the first test block. Refer to panel (a) and (b) of Figure 21. The changes in the ON response seen on Day 1 were consistent with what was reported for Replication Two. N1, marked by a red triangle in the upper two subplots of panel (a), got smaller and P2, marked by a red circle in the lower two subplots of panel (b), got larger. On Day 2, the changes were not as strong as on Day 1, but they were qualitatively the same.

Though Replication One and Replication Two did not show changes in the OFF, the Return Subjects showed significant changes across "test" blocks on both Day 1 and Day 2, with the pattern on each day differing slightly. Based on the "transient" response, panel (a), both days showed that certain components of the OFF seemed to become more negative across "test" blocks. The main negative peak of the OFF is marked by a black diamond in each subplot of Figure 21 (a). Since there were no significant differences between the first "test" block on each day, but there were differences between the first block of Day 2 and the last block of Day1, it would seem that there were no "savings".

The representation must build up again. Hence, Figure 21 has demonstrated another main finding: experience with the stimuli on Day 1 did not have an effect on the Day 2 responses.

Panel (c) shows that there was a change in the steady state response for the Return Subjects over blocks in both amplitude and phase, with no difference between days. The changes were consistent with those indicated for Replication Two (Figure 20). "Test Block 1" had a larger steady state response and this response ran further into the OFF area than it did during the other "test" blocks. The change in the OFF response across "test" blocks described previously may be reflecting this tendency for the steady state to run further into the OFF period for "Test Block 1", which made the OFF look larger overall in that "test" block.

This possibility can be addressed by looking at panel (b), which showed that the OFF response looked nearly identical for the three "test" blocks when the steady state response was removed. The main negative peak of the OFF response, marked by black diamonds in each subplot of Figure 21 (c), occurred at the same time point within each day (118ms after the first omitted stimulus for Day 1 and 122ms for Day2). The amplitude of the main negative response never differed by more than 0.5uV. Differences seen in the "transient" data were not seen in the "notch" data. For example, in the "transient" data, Day 1 had given a significant t-value at 31ms after the first omitted stimulus ($t=-4.56$, $p<0.01$) when comparing "Test Block 1" to "Test Block 3". Panel (a) shows this time point to be picking up on what appears to be a steady state pulse. Panel (b) does not show the same event. In fact, the activity at this time point is very similar

for all three "test" block traces when the data has been "notch" filtered. Panel (b) of Figure 21 seems to confirm that it was the contribution of the steady state response that caused differences in the morphology of the OFF response across "test" blocks for the Return Subjects.

Figure 22 – ON Response "Test" vs "Training" Blocks

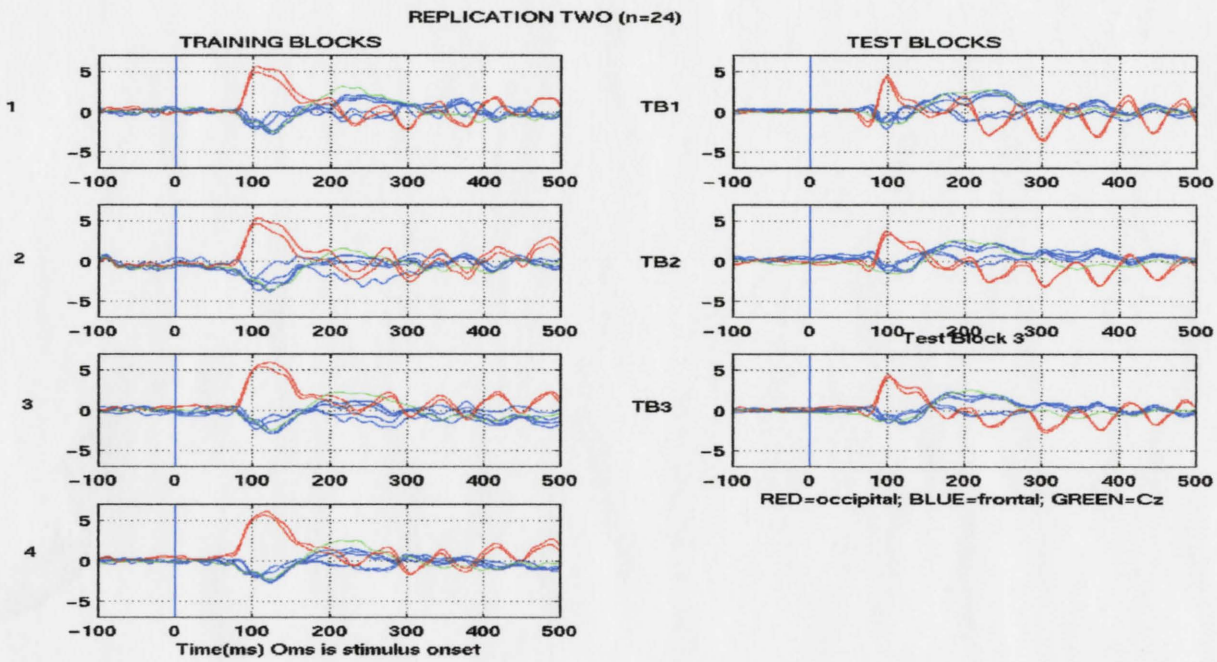


Figure 22 illustrates another main finding. That is, there were differences in the ON response between "test" blocks and "training" blocks. Figure 22 shows Replication Two only. Replication One followed the same patterns, and the differences were even stronger. The "training" blocks can be seen in the left column of Figure 22 and the "test" blocks can be seen on the right. The occipital leads are shown in red, frontal in blue and

the reference, Cz, in green. Again, the data were common referenced and filtered with a low pass filter set at 50Hz.

The ON response that occurred in the "test" blocks was different than that seen in the "training" blocks. The inter-stimulus interval and frequency of stimulation were the same in both block types. The only difference was length of presentation. The ON response in the "test" blocks was much smaller than in the "training" blocks. The ON of the "training" block consistently reached over 5uV, while no component of the "test" block ON reached over 4.5uV. As well, the ON responses differed in morphology. The ON in the "test" blocks were described as having three components: N1, P1 and P2. The "training" block ON seemed best described as one positive peak at 120ms. This one component was more dipolar than the response seen in "test" blocks. The ON in "training" blocks did not change much from blocks 1 to 4, whereas the ON in the "test" blocks showed the changes described earlier: N1 decreased and P2 increased.

Figure 23 – "Test" Block Grand Averages – Replication One and Replication Two

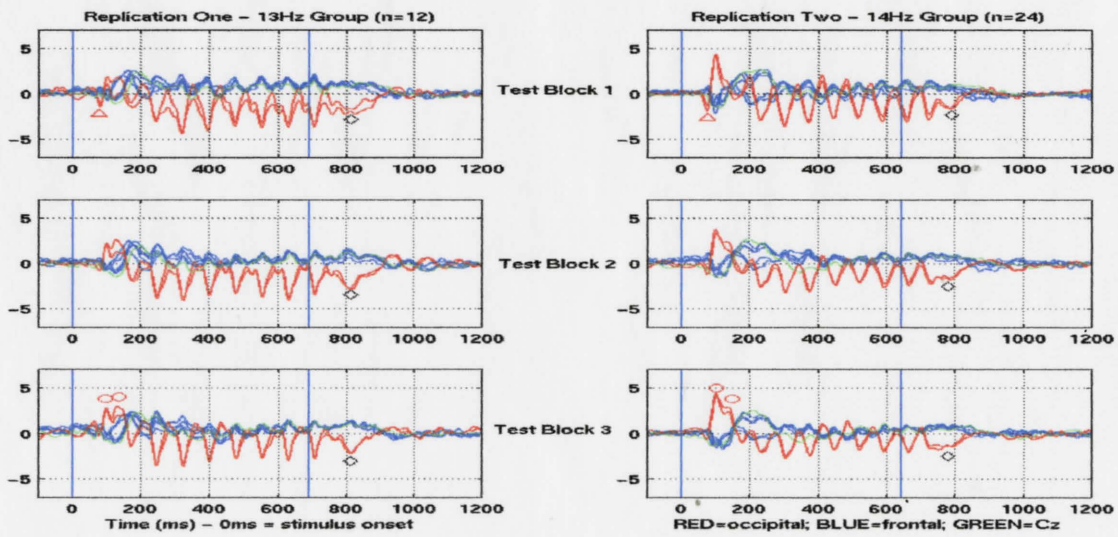


Figure 23 shows the grand averages for the "test" blocks of both Replication One and Replication Two. Replication One is on the left and Replication Two is on the right. It is the "transient" data plotted in each case. The Replication Two data is the same as was plotted in Figure 20 (a). All details, such as electrode traces and denotation of the vertical lines, are consistent with Figure 20. The purpose of Figure 23 is to show that Replication One displayed the same pattern of results as Replication Two. ON and OFF responses were seen right away. The OFF did not change over "test" blocks. The ON, though smaller than the Replication Two ON, showed the same changes across "test" blocks. The differences in the ON between "test" and "training" blocks held up for Replication One as well (Figure not shown).

B) DETAILED ANALYSES

I) ON RESPONSE

The discussion of the ON response in Replication One and Replication Two is based on the "transient" data. That is, the data were filtered with a low pass 50Hz filter.

i) Replication One

Figure 24 - Replication One ON Response

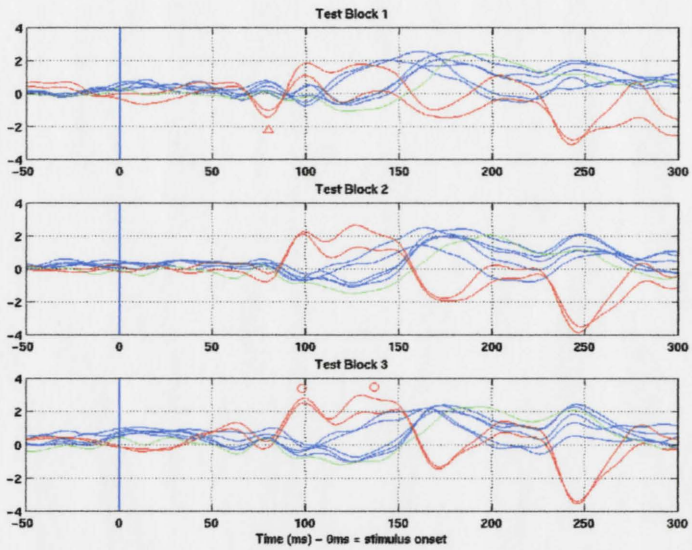
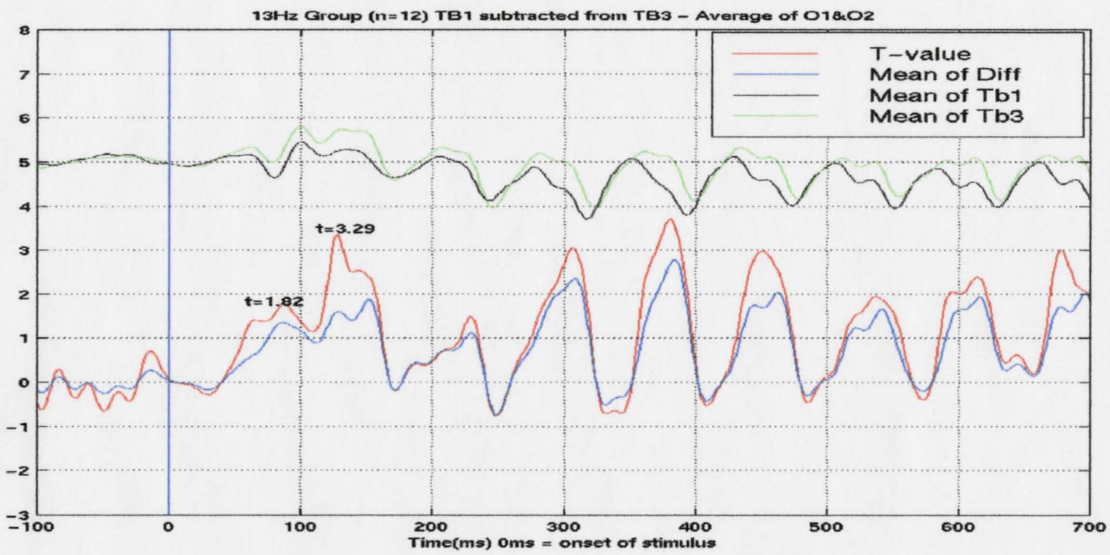


Figure 24 focuses in on the ON response as shown for Replication One in Figure 23. The ON response in Replication One was best described by looking at the occipital electrodes. The occipital leads are shown in red; frontal in blue; and the reference, Cz, in green. The vertical line represents stimulus onset. The O1 and O2 leads showed that the ON was composed of three main components: a negative peak, N1 (shown by a red triangle in the upper subplot of Figure 24) followed by two positive peaks, P1 and P2 (shown by red circles in the lower subplot). There was very little activity until the negative peak occurred around 80ms after stimulus onset. The positive peaks followed

at 100ms and 125ms. The other electrodes did not show any response until 100ms. As the occipital leads went positive, many electrodes, especially the frontal ones, showed a negative peak, which created a dipolar response for the second ON component. The frontal traces then show a long positive peak around 160ms.

Figure 25 - Replication One ON Response
"Test Block 1 Subtracted from Test Block 3"

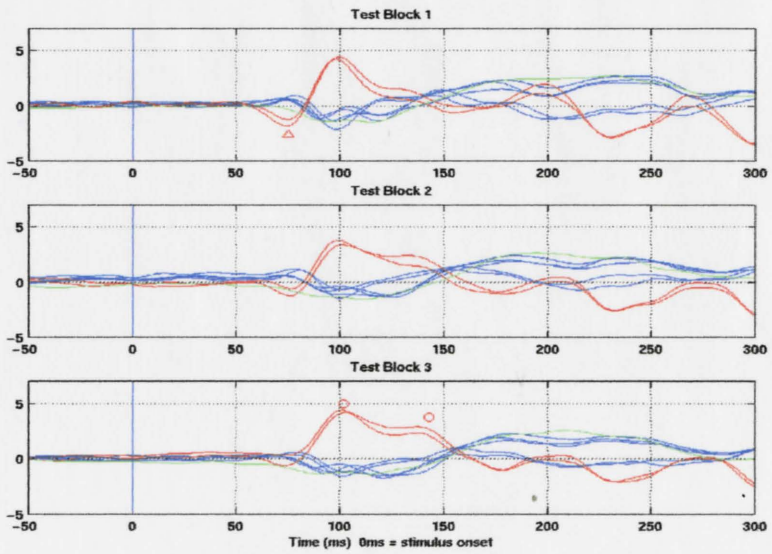


The "difference" wave analysis was done to see if any components of the ON changed as experience with the stimulus was gained (i.e. across "test" blocks). The Replication One group showed that the second positive peak of the ON, which occurred around 125ms, increased with test block. The increase was almost significant ($t=2.25, p<0.05$) when subtracting "Test Block 1" from "Test Block 2" and was significant ($t=3.29, p<0.01$) when subtracting "Test Block 1 from 3". The "TB3-TB1" comparison is shown in Figure 25.

The vertical line in Figure 25 denotes the onset of the stimulus. The two traces plotted together above show the mean of the subject traces, average of O1 and O2, for the "test" blocks being compared. The black and green trace represent "Test Block 1" and "Test Block 3" respectively. The blue trace is the mean of the "difference" traces (TB3-TB1) and the red trace is the plot of the t-values (comparing the difference waves against zero at each point). It can be seen from Figure 25 that the negative peak at 80ms became less negative, but the t-value at that point does not reach significance. The second positive peak became more pronounced and the t-value (t=3.29) is labelled on the figure. Other significant t-values show up later in the figure that reflect that the steady state response was different between the two "test" blocks. It seemed to be larger and more latent in the final "test" block. As well, each steady state event appeared to have two positive peaks.

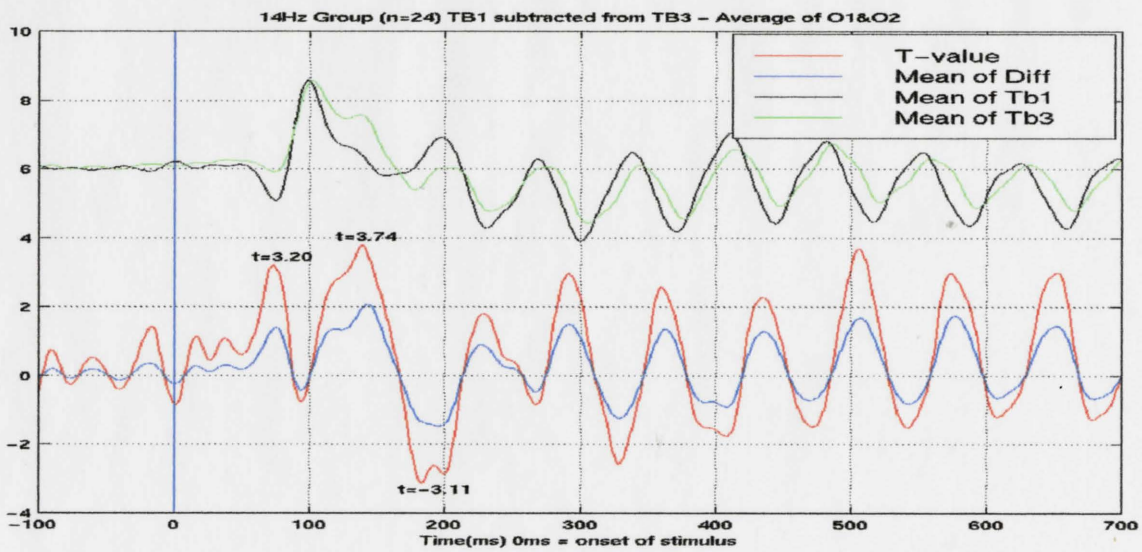
ii) Replication Two

Figure 26 - Replication Two ON Response



Though the ON response for the 14Hz subjects, Figure 26, was larger, the response contained the same components as were described for the 13Hz group. That is, a negative peak, N1 (again marked by a red triangle in the upper subplot), followed by two positive peaks, P1 and P2 (marked by two red circles in the lower subplot), best described the ON response. The latency of two of the peaks differed slightly. The N1 occurred earlier, at 75ms rather than 80ms; the P2 occurred later, at 135ms rather than 125ms. The middle component, P1, still appeared at 100ms. The P2 peak seemed to become more pronounced as it went from "Test Block 1" to "Test Block 3". The other electrodes did not show much activity until 100ms. There was a negative peak in the frontal electrodes at this point, which created a dipolar complex with the positive going occipital electrodes.

Figure 27 - Replication Two ON Response
"Test Block 1 Subtracted from Test Block 3"



As was done for Replication One, the "difference" wave analysis was completed in an attempt to measure changes in the ON across "test" blocks. Replication Two showed the same trends as Replication One: the first negative peak, N1, became less negative; and the second positive peak, P2, became more pronounced. Changes in the ON response are illustrated best by the TB3-TB1 comparison, which is shown in Figure 27. Figure 27 is presented in the same way as Figure 25. The vertical line represents the first omitted stimulus. The two traces plotted together above show the mean of the subject traces, average of O1 and O2, for the "test" blocks being compared. The black and green trace represents "Test Block 1" and "Test Block 3" respectively. The blue trace is the mean of the "difference" traces (TB3-TB1) and the red trace is the plot of the t-values (comparing the difference waves against zero at each point).

For Replication Two, the negative peak (at approximately 70ms), became significantly less negative when "Test Block 1" was subtracted from "Test Block 3". A t-value of 3.20 ($p<0.01$) was seen at 73ms for the TB3-TB1 comparison and is marked in Figure 27. TB2-TB1 and TB3-TB2 both showed peaks in the plot of the t-values at this approximate point, but neither of the t-values reached significance. The TB3-TB1 comparison also showed a significant increase in the second positive peak ($t=3.74$, $p<0.01$) at 135ms. Again, though peaks were seen in the t-value plot at this time point for the other two comparisons, the values did not reach significance.

Another finding that emerged from these "difference" wave comparisons was that the steady state response appeared larger for Test Block 1 and the start of this response,

which seemed larger and earlier in the first block, yielded significant t-values when compared across test blocks. TB2-TB1 gave a value of –3.85 ($p<0.001$) at 185ms (this figure is not shown). TB3-TB1 gave a value of –3.11 ($p<0.01$) at the same time point. Again, this t-value is marked at the appropriate point (185ms) in Figure 27. This is not consistent with what was seen in Replication One in that the "Test Block 1" steady state response was smaller than that of "Test Block 3", though the final block's steady state response is more latent in both cases.

II) OFF RESPONSE

The discussion of the OFF response in Replication One and Replication Two is based on the "transient" data. That is, the data were filtered with a low pass 50Hz filter.

i) Replication One

The OFF response that occurred to the short bursts of stimulation in the "test" blocks, in Replication One, had one obvious component: a negative peak at approximately 120ms after the first omitted stimulus. Figure 23, in the "Overall Picture" section, indicated the OFF response by a black diamond in each subplot. This negative inflection occurred in both occipital leads. The other electrodes demonstrated very little patterned activity after the first omitted stimulus. The morphology of the OFF remained the same for "Test Blocks 1, 2 and 3".

To determine if the OFF response increased as experience with the stimulus was gained, the "difference" wave analysis was again used. Refer back to the "ON Response" discussion for further detail. Three comparisons were done: TB2-TB1, TB3-TB2 and TB3-TB1. A t-test was done on the "difference" waves that were calculated for each

subject (one difference wave per subject per comparison). If the OFF was not changing across blocks, the traces should not be significantly different from zero.

The "difference" wave analysis did not yield any significant values for any of the three comparisons. The TB2-TB1 comparison, not shown here, did show a peak in the t-value plot ($t=-2.43$, $p<0.05$) at 125ms. This is approximately where the main negative peak of the OFF occurred. The t-value indicated that this peak may be getting more negative (i.e. larger), just not to a significant degree, with time or experience. Since the TB3-TB1 and TB3-TB2 comparisons do not give large values, one may think that the changes taking place are doing so quickly. By the third, and even second, "test" block, the representation has been established and further experience with the stimuli has little impact, if any.

ii) Replication Two

Replication Two elicited an OFF to "test" blocks that differed somewhat from that described for Replication One. Refer back to Figure 23. The OFF response changed its morphology across "test" blocks. "Test Block 1" had an OFF that was best described by two negative peaks at 79ms and 143ms, with the second peak being smaller. The second peak is marked by a black diamond in Figure 23. "Test Block 2" also had an OFF composed of two negative peaks (85ms and 140ms). The second negative peak was not only smaller than the first, it was also less pronounced than in "Test Block 1". By "Test Block 3", the OFF is one large negative peak at about 115ms. It was as though the two peaks slowly became one. In all three blocks, the negative peaks seemed to be followed by a long, slow positive wave. Again, this is the OFF as it is seen in the occipital (O1

and O2) electrodes. The "difference" wave analysis did not yield any significant values for the negative peak of the OFF for the three comparisons: TB2-TB1, TB3-TB2 and TB3-TB1.

III) RETURN SUBJECTS

A subset of subjects (n=10) from Replication Two returned 24 hours after the first session to repeat the same procedure. Therefore, there are two days of results, Day 1 and Day 2, and three "test" blocks on each day. The following discussion was simplified by using abbreviations that were consistent with the following example: the first test block on the first day would be abbreviated as "Day1, TB1". Figure 21, in the "Overall Picture" section, showed the "test" blocks from Day 1 and Day2 filtered in three different ways. The analyses reported here were performed on the "transient" data, panel (a), unless otherwise stated. Again, ON and OFF responses were clear with the short burst of stimulation, even after the first "test" block. Questions that were explored for the Return Subjects were as follows. Did the ON and/or OFF responses develop with experience? This question was examined within session and across sessions. Were there any changes in the steady state response? What was the overall effect of returning for a second day?

i) ON Response

The Replication Two subjects showed an ON response (Figure 26) with three components: N1 (75ms), P1 (100ms) and P2 (135ms). The Return subjects, who were drawn from this group, also showed this patterned response to the onset of the short trains of stimulation. The "difference" wave analysis was done to assess whether the same

increases in the ON response across "test" blocks occurred in the smaller subset and if they occurred on Day 2 as well as Day 1. For this smaller group of subjects, the t-value must be greater than 3.250 ($p<0.01$) in order to be considered significant. The TB3-TB1 on Day 1 comparison yielded a significant t-value at 79ms ($t=3.47$, $p<0.01$). Hence, the negative peak (N1) again became less negative. The second positive peak (P2), at 134ms, did not reach significance ($t=2.53$,$p<0.05$) in its increase, but showed the same trend as the 24 subjects in Replication Two. Whereas for Replication Two as a whole, P1 showed no change, the Return subjects showed an increase in P1. This increase was not significant ($t=2.31$,$p<0.05$). Day 2 did not show any significant changes in the ON response across "test" blocks. The negative peak did become less negative, but not significantly so ($t=2.36$,$p<0.05$). The first positive peak actually decreased and the second positive peak showed no change. P2 as a proportion of P1 looks similar (Figure 21 (a)). That is, P2/P1, as a whole, changed as it did on Day 1.

Since Day 2 did not show the increases in the ON in the same way as Day 1, it was thought that perhaps the subjects' ON responses were just bigger to begin with on Day 2. That is, something was gained from the experience on Day 1 and the subjects had already maximized their response. The "difference" wave analysis was done on the "Day2,TB1 – Day1, TB1" comparison. This comparison of "Test Block 1" across days did not yield any significant t-values. As well, "Day2,TB1 – Day1,TB3" gave several values that were either significant or near significant at: 73ms ($t=-2.91$, $p<0.05$); 125ms ($t=-3.85$,$p<0.01$); and 148ms ($t=-3.00$,$p<0.05$). The ON response of the third test block of Day1 was larger in all respects than the first "test" block of Day 2. Therefore, it could

not be concluded that the ON response was larger to begin the session on Day 2 because something was gained from the experience with the stimuli on Day 1.

Two other "test" blocks were compared across days. Perhaps the first "test" blocks were not any different, but the response increased more quickly to its peak amplitude on Day 2. This was not the case. No significant differences were seen when "Test Block 2" was compared across days. There were significant differences in P1 ($t=-4.35, p<0.01$) and P2 ($t=-3.90, p<0.01$), when "Test Block 3" was compared across days. Day 1's "Test Block 3" was significantly larger than that on Day 2 showing that the ON response did not even get as large over the second session.

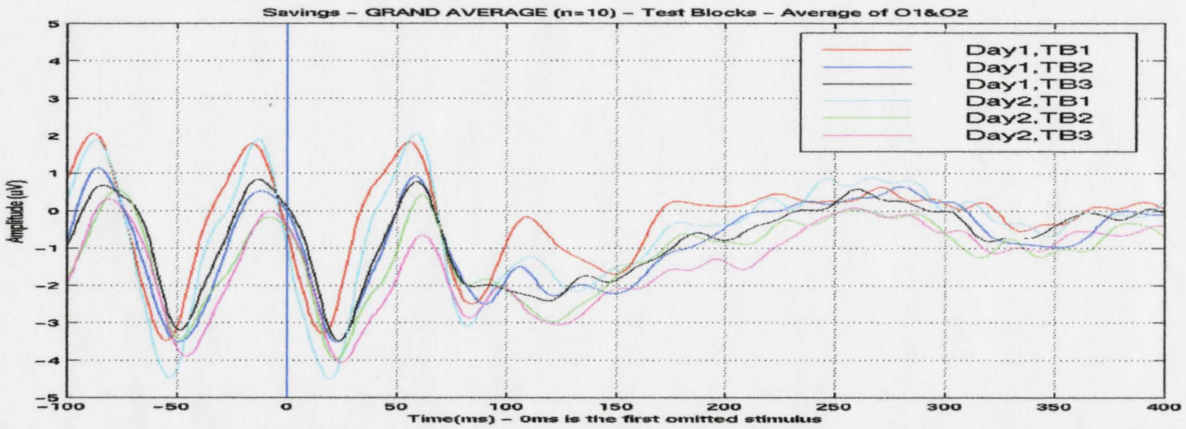
Overall, there seemed to be within session changes that did not repeat to as significant of a degree when the subject returned for a second day. Across session changes did not emerge. The possibility that the ON response would reach its peak more quickly on Day 2 did not hold up. The ON response did not maintain the amplitude it achieved after the first session either. There seemed to be no "savings" from seeing the stimuli on Day 1. However, something did seem to be learned within a session.

iii) OFF Response

Refer back to Figure 21(a) to see the OFF for Day 1 and Day 2 of the Return Subjects. The Return subjects repeated the OFF response pattern that was seen for all of the Replication Two subjects. That is, for Day 1,"Test Block 1" and "Test Block 2" had an OFF characterized by its two negative peaks at 85ms and 145ms. "Test Block 3" had only one negative peak at 121ms; that time point is slightly more latent than the Replication Two OFF of "Test Block 3". Day 2 basically showed this pattern as well.

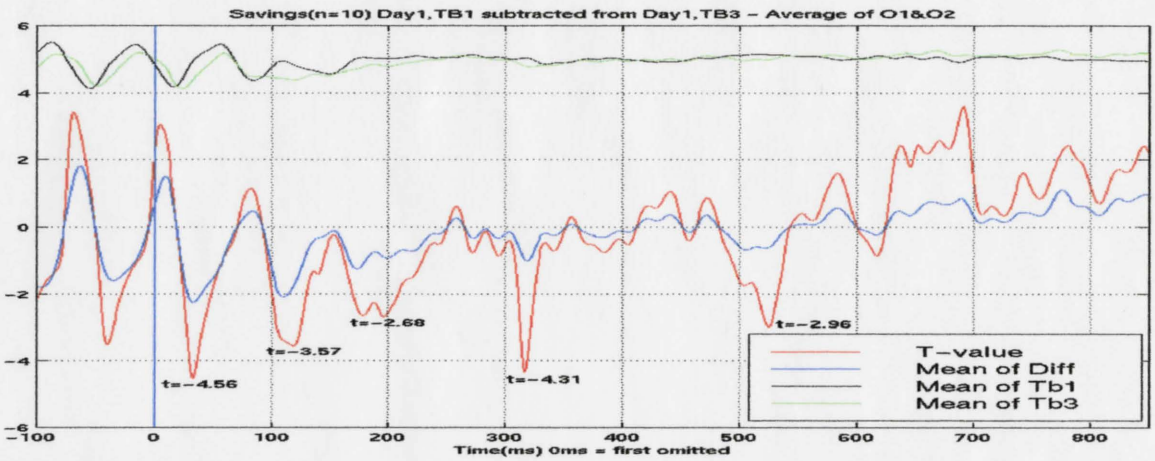
However, the "Test Block 2" OFF had only one negative peak instead of two. In the Return subject data, there seemed to be a late negative peak occurring in the OFF between 330 and 340ms after the first omitted stimulus.

Figure 28 – Return Subjects Grand Average OFF Response "Test" Blocks



The OFF response did not increase across "test" blocks in either Replication One or Replication Two. Did the Return Subjects, who were a subset of the Replication Two subjects, show an increase in OFF response either within session or across session? Figure 28 shows the plot of the 6 traces that represent the grand average for the 10 subjects for the 6 "test" blocks, 3 "test" blocks from each day. The occipital leads, O1 and O2, have been averaged together. From this plot, it did look like there was a change in the OFF around 120ms. However, there did not appear to be an orderly progression from "Day 1, Test Block 1" to "Day 2, Test Block 3".

Figure 29 - Return Subjects OFF Response
"Day1, TB1 Subtracted from Day1,TB3"



The "difference" wave analysis was again used to try and quantify any changes in the OFF response. First, the within session (i.e. within day) comparisons will be discussed. The TB3-TB1 comparison on Day 1, Figure 29, produced significant t-values at several time points: 31ms ($t=-4.56, p<0.01$), 119ms ($t=-3.57, p<0.01$), and 315ms ($t=-4.31, p<0.01$). There were also significant t-values at the corresponding time points for the TB2-TB1 comparison for Day One (not shown). The 31ms point appeared to capture the difference in the size or latency of the steady-state pulse that ran into the OFF period. It seemed to be larger and earlier for the first "test" block. The second significant value, at 119ms, reflected the difference in the morphology of the OFF. For "Test Block 1" this point was between the two negative peaks, while for "Test Block 3" it was almost at the maximal amplitude of the one negative peak. The final value, at 315ms, demonstrated that the late negative peak did become more negative with "test" block. As the larger group that these subjects are drawn from did not show these significant values, this result needs to be interpreted carefully.

The within session, Day 2 comparisons did not repeat the above trend of significant results. The TB3-TB1 comparison gave a significant value at 50ms ($t=-6.29, p<0.001$), which again showed that at least one steady state pulse continued into the OFF and was bigger and earlier for the first "test" block over the last. The other significant value, at 225ms ($t=-3.69$, $p<0.01$), picked up on a difference in the positive going wave that is not too obvious, but precedes the late, negative peak.

Since the changes across "test" blocks on Day 1 did not repeat for Day 2, the question of whether the OFF was just more developed to begin with on Day 2 had to be examined. "Test Block 1" was compared across sessions (Day2-Day1). No significant t-values were found. The subjects did not have a better developed OFF as a result of experience with the stimulus on Day 1.

Figure 30 – Return Subjects – Notch Filtered Data

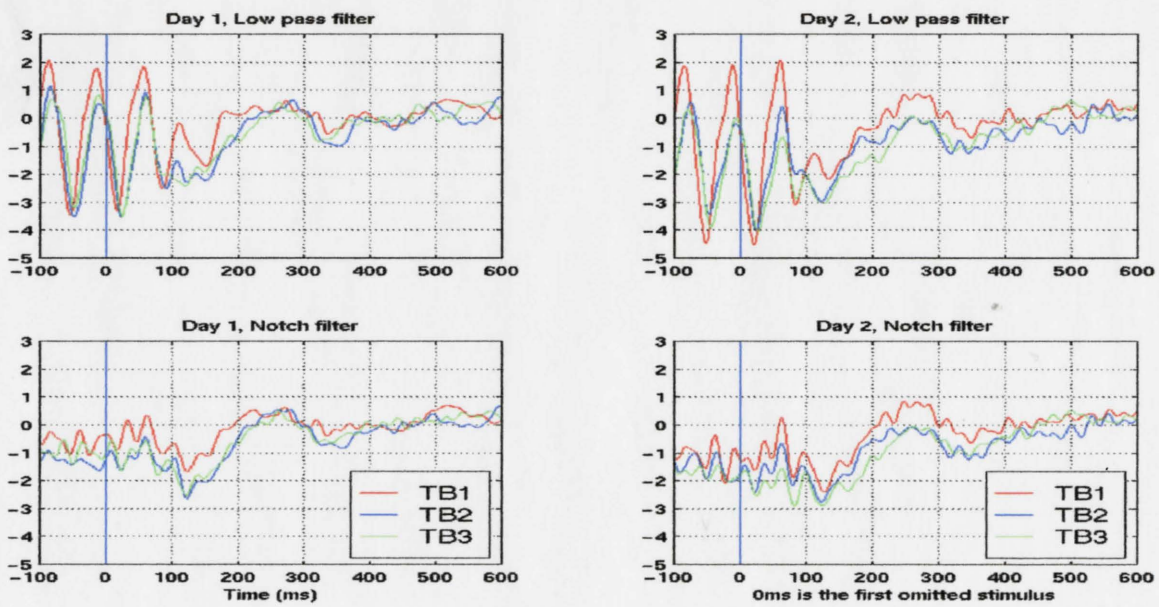
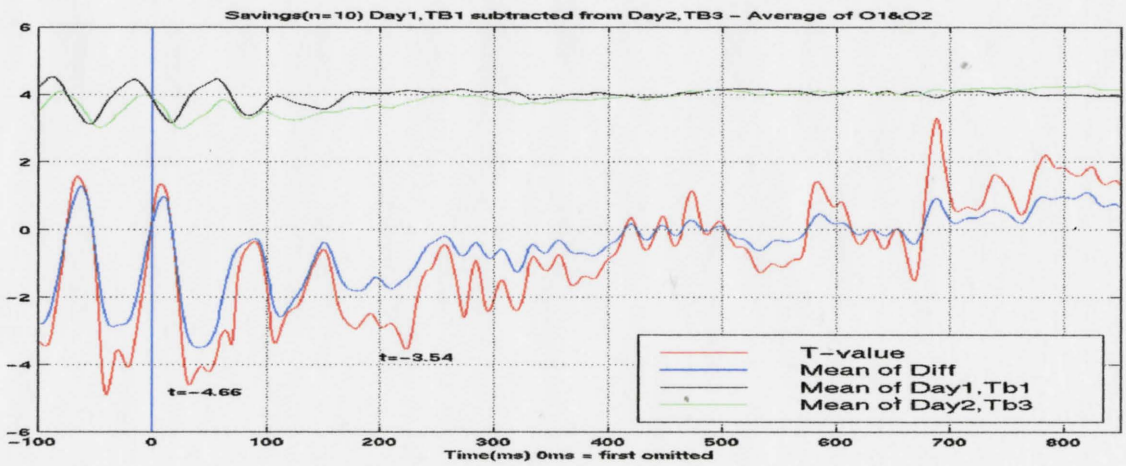


Figure 30 presents the OFF response data for the Return Subjects on Day 1 (left column) and Day 2 (right column). This figure is addressing the issue of how much the steady state response was contributing to the change in the OFF response. The average of O1 and O2 was taken for each "test" block on each day. The colour of the traces remains consistent in each of the four subplots. "Test Block 1" is presented in red; "Test Block 2" in blue; and "Test Block 3" in green. The upper plots of Figure 30 show these three "block" traces for the data when it was filtered with a low pass filter set at 50Hz. The lower two plots show these traces when the data have been "notch" filtered. The data were filtered to remove the 14Hz steady state response. These lower plots showed that the OFF looked nearly identical for the three "test" blocks when the steady state was removed. The time points reported above as providing significant t-values when comparing across "test" block (31ms, 199ms and 315ms on Day1), now look the same. Figure 30 seems to confirm that it was the contribution of the steady state response that caused the differences in the OFF for Return Subjects.

Figure 31 - Return Subjects OFF Response
"Day 1, Test Block 1 Subtracted from Day2, Test Block 3"



Another across session comparison that was of interest was to compare Day2, TB3 to Day1, TB1. What were the differences between the very last block of stimulation compared to the very first? Figure 31 shows the three significant values that result from this comparison: 31ms ($t=-4.66$, $p<0.01$), 106ms ($t=3.32$, $p<0.01$) and 222ms ($t=-3.54$, $p<0.01$). The first point again demonstrated that the steady state pulse that continued into the OFF changed across "test" blocks. The second value could be picking up on the difference in steady state running into the OFF area as well.

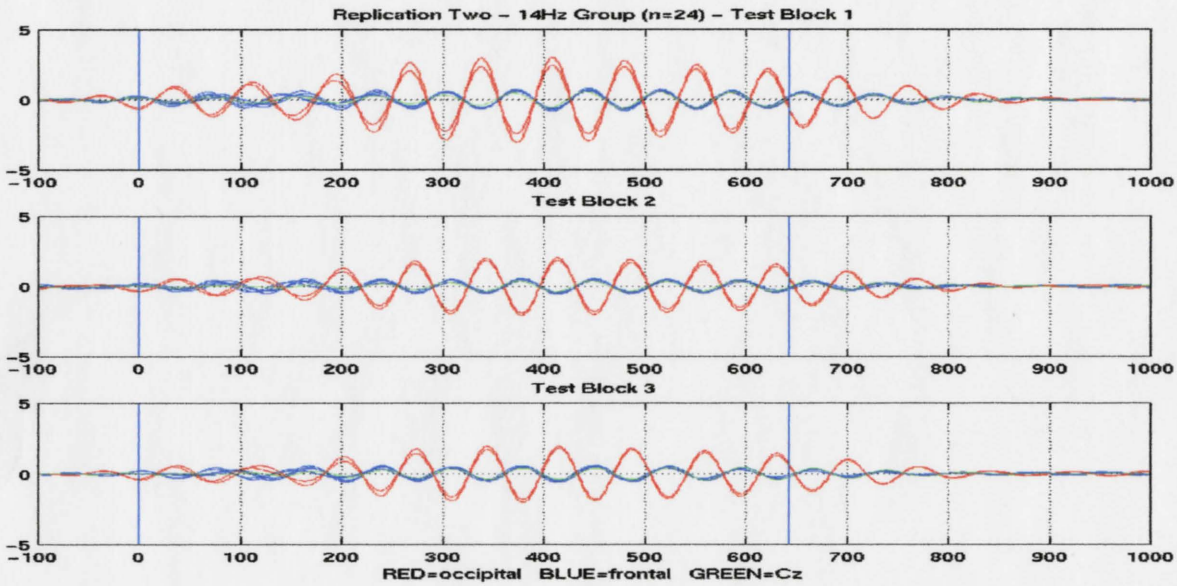
To assist in sorting out what and how the OFF response changed, the Day2,TB1-Day1,TB1 comparison was contrasted to the Day2,TB1-Day1TB3 comparison. Since, there were no significant differences between the first test block on each day, but there were differences between the first block of Day 2 and the last block of Day 1, it would seem that there were no "savings". The representation must build up again. Experience with the stimuli the day before did not have an effect. Although, it seemed that within session, there were changes (at least in the steady state response). As was pointed out earlier, these changes need to be interpreted carefully as they did not repeat within the larger group, Replication Two (n=24).

IV) THE STEADY STATE RESPONSE

The OFF analysis revealed that there were potential changes in the steady state response as the subject gained more experience with the stimulus. Replication Two (n=24) will be used for discussion of this topic. Figure 32 shows the grand average of the "test" blocks for the Replication Two subjects. This is the same data that were plotted

panel (c) of Figure 20. The data, again, have been common referenced, linearly detrended and re-baselined to the last 500ms before stimulus onset. To best examine the 14Hz steady state response, a 10-18Hz band pass filter was used. The filtered data highlights even more that the steady state response runs further into the OFF area after the first test block and that this effect, the running on of the steady-state, decreased as test block increased.

Figure 32 - Replication Two Steady State Response "Test Blocks"



A "root mean square" (RMS) analysis was used to try and quantify the change in steady state response across "test" blocks. The following steps were taken to achieve this analysis. 1) An 800ms area from the first omitted stimulus was chosen. 2) The variance of this interval was taken for "Test Block 1" for each subject. 3) The variance of this interval for "Test Block 3" was computed. 4) These two numbers were subtracted for each subject giving 24 difference numbers. 5) A t-test was done on these numbers. 6)

Were these numbers significantly different from zero (with n-1 degrees of freedom)? Significant t-values will be (doing it as a two-tailed test and assuming no direction): $p<0.01$, $t=2.807$; and $p<0.001$,$t=3.767$.

Again, the average of O1&O2 was used. The results of the analysis were that: TB1-TB3 was not a significant comparison ($t=2.5474$); the TB1-TB2 comparison yielded a t-value of 3.2062 which is significant at the 0.01 level; and the TB2-TB3 comparison gave a t-value of 0.2760 which is not significant. So it seems that "Test Block 2 and 3" were most similar and it was "Test Block 1" that was so different. Replication Two showed that the steady state response was largest in "Test Block 1" and decreased across "test" blocks. It seemed also that the steady state grew faster and took longer to die out in "Test Block 1". The Return Subjects, were a subset of the Replication Two subjects, repeated this pattern on both Day1 and Day2.

DISCUSSION

The OFF response

An OFF response occurred in the very first "test" block of the experiment. The fact that it is seen right away and does not change much over the course of the experiment answers the questions posed at the end of Experiment One. The increase in the size of the OFF response as repetition rate was increased in Experiment One, was not likely due to the increased amount of extra stimulation at the higher repetition rates, but rather to the nature of the repetition rate itself. Very short bursts of 13Hz and 14Hz stimulation (~600ms) produced an OFF response in Experiment Two whereas 6-second trains of 1.5Hz stimulation did not produce an OFF response in Experiment One. The equated experience with the stimuli (9 pulses in each case) does not have the same effect. The OFF seems to depend on repetition rate. The 13Hz or 14Hz stimulation is in the steady state range while the 1.5Hz stimulation is not. Perhaps it is the inability to fully recover between stimuli that causes a release from responding to be seen at the end of a steady state train of stimulation.

The "test" block OFF response was a negative peak at 140ms. The OFF response at 13Hz in Experiment One also showed this component. The later components in the OFF response of Experiment One do not emerge in the "test" blocks. The short bursts of stimulation may not be optimal for seeing these components.

The ON response

The ON response did change over "test" blocks. The N1 diminished and the P2 increased (P1 remained the same). The P2 enhancement was the most robust change as it was significant in both Replication One and Replication Two. The change in the ON response across the experiment could reflect habituation. An inhibitory response could also be decreasing from the repeated exposure to the same stimulus, and release from inhibition could be reflected in the growth of the P2 component. The habituation explanation does not eliminate the possibility that something was learned about the stimulus during the session. The Condon & Weinberger (1991) work, discussed in the Introduction, showed that repeated exposure to a stimulus resulted in a very specific decrease in neuronal firing only to the frequency of the repeatedly presented tone. The change in response was not due simply to fatigue.

Habituation may not be the best explanation however. The ON response to the "training" blocks remained constant over the experiment (Figure 22). The "training" blocks involved the same stimulation (either 13Hz or 14Hz depending on Replication) only in longer trains (6 seconds). The "training" blocks were interspersed with the "test" blocks. So, if the "test" blocks were changing because of habituation, this should be carried over to the "training" blocks. It seems that the ON response was altered as more experienced was gained with the stimulus.

The morphology of the "training" block ON response differed from the "test" block ON response. The ON response in the "test" blocks was much smaller than in the "training" blocks. Though the "test" block ON response was comprised of three

components (N1, P1 and P2), the "training" block ON response was one large positive peak. These differences are interesting in that the ON is occurring to the exact same event, a 10ms flash from the same LED. The length of the pause at the end of each train is the same. The duration of the train seems to affect the characteristics of the ON response. Perhaps if the first couple trains were examined between the "test" and "training" blocks, the ON responses would look similar. Repeated exposure to the trains could develop a representation of the stimulus that reflects train duration. Bullock et al. (1994) concluded that a "major category of sensory response characteristics, besides the classical ones, is that of dependence upon recent history of iterative events, including their intervals, delays and omissions ..." (p.52). The difference in ON response described here may reflect this response characteristic.

When subjects returned for a second session, the changes in the "test" block ON response were not maintained. The subjects' ON response in the first "test" block of Day 2 looked as it did in the first "test" block of Day 1. The subjects' response had recovered within the 24hour period. Though the changes occurred rather quickly (within a 50 minute session), they did not have a long retention interval.

Within-session changes were seen on Day 2 that, though not as strong, were qualitatively the same as on Day 1. Condon & Weinberger (1991) ran additional sessions on some subjects in their habituation studies. Additional sessions that used a different frequency as the repeated stimulus (than the frequency that was originally used) resulted in a frequency-specific decrease. If the same frequency was used as in the first session, no decrements developed. Condon & Weinberger concluded that further "habituation-

induced decrements at the REP (repeated stimulus) frequency in RFs are not likely if the same frequency is used" (p.425). Using the same frequency of stimulation in a second session, this experiment showed within-session changes on Day 2. Changes that extended or were greater than that seen on Day 1 did not occur.

The steady state response

The steady state response also changed over "test" blocks. The response became smaller and more latent with the progression from "Test Block 1" to "Test Block 3". The steady state responses in the "test" blocks of Day 2 were comparable to their corresponding "test" blocks on Day 1. Nothing seemed to be gained from the experience on Day 1. Subjects' responses recovered to the level shown in the first "test" block of Day 1 and the changes built from there. This relates to the discussion of the ON response. Subjects seem to learn something about the stimulus within session but this does not carry over to the next session.

Possible ways to improve the effects

Effects may have been longer lasting if greater demands were placed on the subject. The subjects were only required to attend to the stimuli, with attention measured by a simple counting task. If it were required that discriminative judgements were made about the stimuli, perhaps the within-session effects would have been larger and the effects may have still been present on the second day. Discriminative judgements require further processing of the stimuli.

Through discriminative judgements, behavioural performance or otherwise, greater effects may have been seen if the stimuli were made more behaviourally relevant to the subject. Ahissar et al. (1992) measured the effect of one neuron on another in the behaving monkey. Some conditioning trials required the monkey to respond to a change in the tone (US) which was presented after the CS neuron fired. In other conditioning trials, the monkey was not rewarded and did not perform after presentation of the US. Conditioning trials that involved behaviour always showed stronger alterations in the connection between the two neurons than conditioning trials without behaviour. Ahissar et al. concluded that contingency can lead to a change in strength of connection, but the change should be stronger if behavioural relevance is involved. Edeline et al. (1993) showed that classical conditioning, involving only 30 tone-shock pairings, can lead to receptive field plasticity that lasts as long as 8 weeks. A shock is a potent stimulus that it is important for the animal to learn quickly about and remember. Change in responses can be longer lasting when the stimuli take on more significance.

Very simple stimuli were used in this experiment. They were used because Bullock et al. had used simple stimuli and they were convenient. Short flashes are novel and not something that one is exposed to or required to evaluate on a daily basis. An examination of the development of a novel representation was allowed. However, effects may have been greater if more complex stimuli were used. The visual system is required to continually analyze and adjust to very complex stimuli. Stimuli that are more consistent with what is demanded of the visual system, may have elicited longer lasting changes as a result of experience.

CHAPTER FOUR

GENERAL DISCUSSION

Buonomano & Merzenich (1998) discussed three levels of analysis at which cortical plasticity has been studied. "Synaptic plasticity", usually done in slice preparations, examines synaptic events underlying phenomena such as long term potentiation (LTP) or depression (LTD) of excitatory post-synaptic potentials (EPSPs). "Cellular conditioning" looks at selective responses of single neurons within the living organism. Typically, the investigations are of the effects of short term (minutes or tens of minutes) conditioning procedures. "Representational plasticity" measures the changes in distributed responses in the sensory cortices after manipulation of inputs (e.g. lesions) or behavioural training. Studies at this level generally take their measurement of response change hours or months after the manipulation or after days or weeks of intense behavioural training. The experiments reported here are unique in that they attempted to measure the changes in distributed responses, as in "representational plasticity" studies, but over a very short time scale, as is done at the level of single neurons in "cellular conditioning". Subjects were intact, adult humans and measurements of generalized neuronal response were done non-invasively with EEG.

The experiments reported here are also unique in that they examine plasticity induced by non-associative procedures rather than associative procedures. Understanding how neuronal responses change due to repetitive stimulation may be important in

understanding change in response after explicit correlation between sensory input and behaviourally relevant task events. Different mechanisms are thought to be responsible for the plasticity that results from the two procedures. The synaptic mechanisms for long term potentiation (LTP) and depression (LTD) are thought to mediate associative plasticity (Buonomano & Merzenich, 1998). Habituation is thought to mediate non-associative plasticity (Cruikshank & Weinberger, 1996). Since both procedures induce patterning of neuronal response and attentional processing, the mechanisms could overlap.

Buonomano & Merzenich (1998b) have labelled synaptic dynamics that are modified quickly by repetitive stimulation and then recover quickly, "short-term plasticity". It could be argued that Experiment Two was a demonstration of short-term plasticity. Repetitive stimulation was delivered to the subject throughout a 50-minute session. Neurons altered their firing over the experimental session as experience with the stimuli was increased. As a result, changes were seen in the ON response and in the steady-state response. Whether the changes were due to habituation or some other mechanism, something changed over the session and was reflected in neuronal activity. The recovery was rapid in that there was no effect of the session 24 hours later. Recovery, perhaps, occurred much sooner but there were no measurements taken between these times.

One must question how it is that such short term plasticity could take place when it has been shown that LTP induction in the neocortex requires lengthy conditioning procedures. For example, Racine et al. (1995) demonstrated a persistent form of LTP in

chronically prepared rats. High frequency trains of stimulation were applied 30 times each day for 25 days. LTP was seen after about 5 days of the procedure. The length of time for induction of LTP is very different from the findings of Experiment Two, where changes in neuronal response were seen within a 50-minute session. The time course of the changes in Experiment Two were very short and had receded within 24 hours. LTP persisted for at least 4 weeks in the Racine et al. work. There are several possible reasons that such differences exist. First, Racine et al. (1995) measured from a single bipolar electrode implanted in rats, while the studies reported here measured electrical activity across the whole head of humans. Perhaps the changes seen in Experiment Two cannot be realized by a single channel recording. As well, humans have very well developed sensory cortices that produce large responses. These responses are known to be affected by attentional processes and therefore, seem to indicate there is some cognitive component to the measured response. This may be fundamentally different from what is measured with LTP. Also, Racine et al. recorded callosal-neocortical field potentials and Experiment Two recorded the activations of thalamocortical projections. The corpus callosum links the cortical neurons between the two hemispheres. The thalamus is a sensory relay station. The neuronal activity of the connections from these two different structures, and their capacity to change, could reflect their different functional requirements.

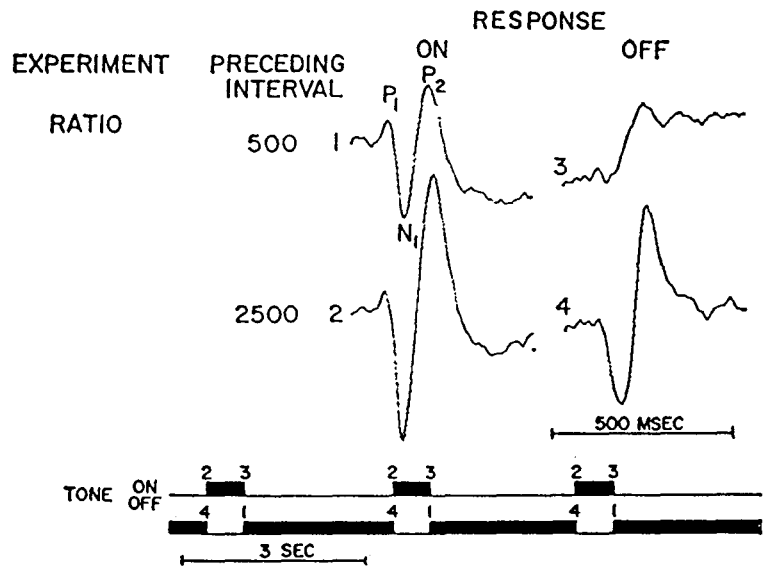
Plasticity occurring on a short time scale may be important for several reasons. First, because neuronal response to its inputs is modified by these short term processes, these processes could be involved in the longer lasting changes of synaptic efficacy

induced by associative procedures (Buonomano & Merzenich, 1998). Second, short-term forms of plasticity may be responsible for processing temporal information. Differences in population responses (caused by successive stimuli activating different but overlapping networks of neurons) "can be used to code for temporal features of stimuli, such as duration, interval and order" (Buonomano & Merzenich, 1998b). Third, short-term plasticity may be important to the rapid learning about stimuli that is required when interacting in the world. Tovee et al. (1996), who showed that neuronal firing to an ambiguous image was increased after exposure to the unambiguous image, argued that the rapid visual learning was an important part of the system that learns about rapidly changing views of objects.

APPENDIX I

Evoked Responses to Tone Onset and Cessation

Figure from Pfefferbaum, Buchsbaum and Gips (1971)



The upper panel shows the ON and OFF response to tone onset and cessation when a 500ms tone is followed by a 2500ms pause. The lower panel reverses this situation. It shows the ON and OFF responses elicited by a 2500ms tone burst followed by a 500ms pause. The N1-P2 complex, labelled for the ON response in the upper panel, can be seen for both the ON and OFF response. The morphology of the responses is quite similar. The OFF response is of smaller amplitude than the ON response, with the effect more pronounced when a short tone burst is delivered.

APPENDIX II

Experiment One

Subjects were instructed to count the number of OFF periods occurring in each block of stimulation in Experiment One. The OFF period was the approximate 2-second pause following the 6-second train of stimulation. There were nine blocks and 40 trains per block. Hence, there were 40 OFF periods to be counted during each block. The following tables document the number of OFFs reported by each subject for each block. A cell containing "dc" indicates that the subject did not count during that block of stimulation.

VISUAL DATA									
	Blo cks								
Subjects									
subject 1	45	51	48	37	40	45	40	40	40
subject 2	47	36	40	41	41	46	43	40	40
subject 3	43	42	39	39	42	39	41	40	40
subject 4	40	39	40	40	40	40	40	41	41
subject 5	40	38	40	40	40	37	47	38	40
subject 6	39	41	43	39	36	40	39	36	41
subject 7	41	40	40	40	39	38	40	40	40
subject 8	40	41	40	39	38	41	40	40	42
subject 9	dc	40	41	38	40	41	40	39	40
subject 10	39	39	39	36	38	40	38	dc	37
subject 11	38	37	35	37	34	42	39	43	41
subject 12	30	45	42	41	38	40	37	42	40
subject 13	20	35	38	40	41	40	39	40	40
subject 14	30	36	25	37	29	40	32	36	34

AUDITORY DATA									
	Blo cks								
Subjects									
subject 1	40	40	40	40	40	40	40	40	40
subject 2	40	40	40	40	40	40	40	40	40
subject 3	42	40	39	40	42	41	44	43	41
subject 5	26	40	40	40	40	40	40	40	40
subject 6	39	39	41	34	43	44	34	44	40
subject 8	40	40	40	40	40	40	40	40	40
subject 10	40	40	40	40	41	42	40	41	40
subject 11	40	40	40	40	40	41	40	40	40
subject 14	40	40	40	40	40	40	40	40	40
subject 15	40	40	40	40	40	40	40	40	40

SOMATOSENSORY DATA									
	Blo cks								
Subjects									
subject 5	37	40	37	40	40	42	40	43	40
subject 6	46	47	50	44	61	67	53	55	50
subject 7	dc	dc	39	44	45	43	45	43	41
subject 8	41	41	40	40	40	40	40	40	40
subject 9	35	39	40	40	40	41	40	41	42
subject 10	39	40	40	40	39	40	40	40	40
subject 12	40	40	40	41	40	40	40	41	40
subject 13	41	40	39	41	43	41	39	42	43
subject 14	38	40	40	38	41	39	40	40	41
subject 15	14	37	40	35	47	40	43	46	47
subject 16	39	41	39	40	37	39	40	40	40
subject 17	40	38	39	38	40	40	43	41	45

APPENDIX III

Experiment Two

Subjects were instructed to count the number of OFF periods occurring in each block of stimulation in Experiment Two. The OFF period was the approximate 2 second pause following the 6 second or 600ms (depending on whether it was a "test" block or a "training" block) train of stimulation. There were seven blocks, three "test" blocks and four "training" blocks. "Test" blocks were comprised of 100 trains of stimulation (therefore, 100 OFFs to count) and "training" blocks were comprised of 60 trains of stimulation (therefore, 60 OFFs to count). The following tables document the number of OFFs reported by each subject for each block in both Replication One and Replication Two, including the Return Subject data. A cell containing "dc" indicates that the subject did not count during that block of stimulation.

REPLICATION ONE							
				Blocks			
Subjects	test	training	training	test	training	training	test
subject 1	101	52	56	100	56	69	103
subject 2	100	60	60	100	60	60	100
subject 3	100	56	60	100	60	51	100
subject 4	100	60	60	100	60	60	100
subject 5	103	57	58	101	60	60	100
subject 6	100	60	64	99	62	61	101
subject 7	100	55	56	100	67	62	89
subject 8	100	60	60	100	60	60	100
subject 11	79	60	60	98	60	60	97
subject 12	95	60	63	100	75	62	93
subject 31	100	60	60	100	60	60	99
subject 32	100	64	60	87	64	66	112

REPLICATION TWO							
	Blocks						
Subjects	test	training	training	test	training	training	test
subject 13	100	60	60	100	60	58	100
subject 14	100	60	62	100	60	60	100
subject 15	100	64	62	102	62	63	98
subject 16	100	67	61	100	61	63	100
subject 17	100	60	59	100	60	60	100
subject 18	100	61	61	100	110	53	100
subject 20	101	61	59	101	59	63	101
subject 21	100	60	59	100	60	60	100
subject 22	101	60	60	99	60	60	100
subject 23	101	60	61	100	61	60	90
subject 24	100	60	58	100	61	60	101
subject 25	102	60	62	99	61	70	98
subject 26	100	60	60	100	60	59	100
subject 27	100	60	63	100	55	63	101
subject 28	100	70	61	100	60	59	100
subject 29	87	59	61	100	60	63	100
subject 33	100	60	59	100	64	64	100
subject 34	100	60	60	101	60	60	100
subject 35	100	59	60	101	61	60	99
subject 36	100	60	60	99	61	60	100
subject 37	100	58	62	98	58	57	99
subject 38	100	60	60	100	67	60	100
subject 39	100	60	59	101	60	59	100
subject 40	100	61	61	112	60	60	100

RETURN SUBJECTS							
	Blocks						
Subjects	test	training	training	test	training	training	test
return 15	100	62	64	99	63	61	102
return 18	100	60	60	100	64	69	101
return 28	100	60	60	100	60	60	100
return 33	100	63	61	100	59	67	100
return 35	99	62	60	99	61	61	99
return 36	100	60	60	100	59	59	99
return 37	99	59	58	99	58	59	99
return 38	100	60	60	100	60	60	100
return 39	100	60	59	100	59	59	100
return 40	100	60	60	100	60	60	100

REFERENCES

Ahissar, E., Vaadia, E., Ahissar, M., Bergman, H., Arieli, A. and Abeles, M. (1992). Dependence of cortical plasticity on correlated activity of single neurons and on behavioural context. Science, 257, 1412-1414.

Allard, T., Clark, S.A., Jenkins, W.M. and Merzenich, M.M.. (1991). Reorganization of somatosensory area 3b representations in adult owl monkeys after digit syndactly. Journal of Neurophysiology, 66(3), 1048-1058.

Baier, Bernhard. (1997). On and Off responses in the human somatosensory evoked potential. Undergraduate Thesis. McMaster University, Department of Psychology.

Bakin, J.S. and Weinberger, N.M. (1990). Classical conditioning induces CS-specific receptive field plasticity in the auditory cortex of the guinea pig. Brain Research, 536, 271-286.

Bullock, T.H., Karamursel, S., Achimowicz, J.Z., McClune, M.C., and Basar-Eroglu,C. (1994). Dynamic properties of human visual evoked and omitted stimulus potential. Electroencephalography and Clinical Neurophysiology, 91, 42-53.

Buonomano, D.V. and Merzenich, M.M. (1998). Cortical plasticity: from synapses to maps. Annual Review of Neuroscience, 21, 149-186.

Buonomano, D.V. and Merzenich, M.M. (1998b). Net interaction between different forms of short-term synaptic plasticity and slow IPSPs in the hippocampus and auditory cortex. Journal of Neurophysiology, 80, 1765-1774.

Calford, M.B. and Tweedale, R. (1988). Immediate and chronic changes in responses of somatosensory cortex in adult flying-fox after digit amputation. Letters to Nature, 332, 446-448.

Cody, T.D.R. and Townsend, G.L. (1973). Some physiologic aspects of the averaged vertex response in humans. Audiology, 12, 1-13.

Condon, C.D. and Weinberger, N.M. (1991). Habituation produces frequency-specific plasticity of receptive fields in the auditory cortex. Behavioral Neuroscience, 105(3), 416-430.

Cruikshank, S.J. and Weinberger, N.M. (1996). Evidence for the hebbian hypothesis in experience-dependent physiological plasticity of neocortex: a critical review. Brain Research Reviews, 22, 191-228.

Davis, H., Osterhammel, P.A., Wier, C.C. and Gjerdingen, D.B. (1972). Slow vertex potentials: interactions among auditory, tactile, electric and visual stimuli. Electroencephalography and Clinical Neurophysiology, 33, 537-545.

Diamond, M., Huang, W. and Ebner, F. (1994). Laminar comparison of somatosensory cortical plasticity. Science, 265, 1885-1888.

Edeline, J-M., Pham, P., and Weinberger, N.M. (1993). Rapid development of learning-induced receptive field plasticity in the auditory cortex. Behavioral Neuroscience 107(4), 539-551.

Elbert, T., Pantev, C., Wienbruch, C. Rockstroh, B. and Taub, E.. (1995). Increased cortical representation of the fingers of the left hand in string players. Science, 270, 305-307.

Gilbert, C.D. and Wiesel, T.N. (1992). Receptive field dynamics in adult primary visual cortex. Nature, 356, 150-152.

Hari, R., Pelizzone, M., Makela, J.P., Hallstrom, J. Leinonen, L. and Lounasmaa, O.V. (1987). Neuromagnetic responses of the human auditory cortex to on- and offsets of noise bursts. Audiology, 26(1), 31-43.

Hillyard, S.A. and Picton, T.W. (1978). ON and OFF components in the auditory evoked potential. Perception&Psychophysics, 24(5), 391-398.

Kaas, J.H., Krubitzer, L.A., Chino, Y.M., Langston, A.L., Polley, E.H. and Blair, N. (1990). Reorganization of retinotopic cortical maps in adult mammals after lesions of the retina. Science, 248, 229-231.

Kalaska, J. and Pomeranz, B. (1979). Chronic paw denervation causes an age-dependent appearance of novel responses from forearm in "paw cortex" of kittens and adult cats. Journal of Neurophysiology, 42(2), 618-633.

Karni, A. and Sagi, D. (1991). Where practice makes perfect in texture discrimination: evidence for primary visual cortex plasticity. Proceedings of the National Academy of Science, 88, 4966-4970.

Marlin, S.G., Douglas, R.M. and Cynader, M.S. (1991). Position-specific adaptation in simple cell receptive fields of the cat striate cortex. Journal of Neurophysiology, 60(5), 1769-1784.

Merzenich, M.M., Kaas, J.H., Wall, J., Nelson, R.J., Sur M. and Felleman, D. (1983). Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation. Neuroscience, 8(1), 33-55.

Merzenich, M.M., Nelson, R.J., Stryker, M.P., Cynader, M.S., Schoppmann, A. and Zook, J.M. (1984). Somatosensory cortical map changes following digit amputation in adult monkeys. The Journal of Comparative Neurology, 224, 591-605.

Mushin, J., Hogg, C.R., Dubowitz, L., Skouteli, H. and Arden, G.B. (1984). Visual evoked responses to light emitting diode (LED) photostimulation in newborn infants. Electroencephalography and Clinical Neurophysiology, 58, 317-320.

Pantev, C., Oostenveld, R., Engelien, A., Ross, B., Roberts, L.E., and Hoke,M. (1998). Increased auditory cortical representation in musicians. Letters to Nature, 392, 811-813.

Pfefferbaum, A., Buchsbaum, M. and Gips, J. (1971). Enhancement of the average evoked response to tone onset and cessation. Pyshcophysiology, 8(3), 332-339.

Racine, R.J., Chapman, C.A., Trepel, C., Teskey, G.C., and Milgram, N.W. (1995). Post-activation potentiation in the neocortex. IV. Multiple sessions required for induction of long-term potentiation in the chronic preparation. Brain Research, 702, 87-93.

Ramachandran, V.S., Stewart, M. and Rogers-Ramachandran, D.C. (1992). Perceptual correlates of massive cortical reorganization. Neuroreport, 3(7), 583-586.

Recanzone, G.H., Merzenich, M.M., Jenkins, W.M., Grajski, K.A. and Dinse, H.R. (1992). Topographic reorganization of the hand representation in cortical area 3b of owl monkeys trained in a frequency discrimination task. Journal of Neurophysiology, 67(5), 1031-1056.

Recanzone, G.H., Schreiner, C.E. and Merzenich, M.M. (1993). Plasticity in the frequency representation of primary auditory cortex following discrimination training in the adult owl monkey. The Journal of Neuroscience,13, 87-103.

Regan, D. (1989). Human Brain Electrophysiology: Evoked Potentials and Evoked Magnetic Fields in Science and Medicine. New York: Elsevier Science Publishing Co., Inc.

Robertson, D. and Irvine, D.R.F. (1989). Plasticity of frequency organization in auditory cortex of guinea pigs with partial unilateral deafness. The Journal of Comparative Neurology, 282, 456-471.

Schweitzer, P.K. and Tepas, D.I. (1974). Intensity effects of the auditory evoked brain response to stimulus onset and cessation. Perception and Psychophysics, 16(2), 396-400.

Tovee, M.J., Rolls, E.T., and Ramachandran,V.S. (1996). Rapid visual learning in the neurones of the primate temporal visual cortex. Cognitive Neuroscience, 7, 2757-2760.

Weinberger, N.M. (1995). Dynamic regulation of receptive fields and maps in the adult sensory cortes. Annual Review of Neuroscience, 18, 129-158.

Wang, X., Merzenich, M., Sameshima, K. and Jenkins,W. (1995). Remodelling of hand representation in adult cortex determined by timing of tactile stimulation. Nature, 378, 71-75.